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GLYCOGEN DISEASE

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1 INTRODUCTION

In recent years the interest of biochemists, clinicians and pathologists in the rôle of glycogen in normal and pathological metabolism has greatly increased. This is partly due to the recent description of a series of morbid pictures in which the metabolism of glycogen is abnormal as demonstrated by its accumulation in large amounts in certain organs. A further abnormality is the great stability of this glycogen after death. Above all, the striking peculiarity in these morbid pictures is the great hypertrophy of one or more organs in which the excess of glycogen is found. Among the various causes of hypertrophy of different organs, the accumulation of glycogen must be considered, particularly among the disturbances manifesting themselves shortly after birth. Glycogen disease is a disturbance which merits the consideration of pediatricians, in particular, it seems likely that the study of this condition will add materially to our knowledge of the physiology and pathology of carbohydrate metabolism, and will increase our insight into several other diseases of childhood.

In most cases observed up to the present the liver has been chiefly involved. Owing to the central rôle of the liver in carbohydrate metabolism and the peculiar conduct of glycogen in this disease the clinical study of these cases of "glycogen liver," as might be expected, has already given striking results.

In 1928 we were able to report an extensive clinical study of a case which may be regarded as the first case of "glycogen liver", it concerned a boy in whom an enlargement of the liver had been found shortly after birth. We then came to the conclusion that in all probability we had to deal here with a condition in which glycogen had accumulated in the liver and perhaps also in the muscles, but in which this glycogen could be mobilized only with great difficulty. Then, in 1929, the article of *von Gierke* was published on hypertrophy of organs (liver and kidneys) caused by accumulation of glycogen, this accumulation had been found post mortem in cases which clinically had not been recognized. In that year also the article of *Schonhermer* appeared on the chemical investigations performed in these cases.

In 1932 and 1933, when we further reported on this condition and surveyed the literature, only a small number of such cases were known. Since then many publications have appeared and the number of new cases has greatly increased. Therefore, before giving an extensive clinical and pathological discussion of the literature of this new disease, we shall review briefly some present day conceptions about the physiology and pathology of glycogen.

Eighty years have passed since *Claude Bernard* discovered glycogen. This was one of the most fundamental discoveries in the field of carbohydrate metabolism. *Claude Bernard's* investigations clearly demonstrated the important rôle of the liver in its metabolism. Since then glycogen has taken an important place in physiology and pathology. In some respects our conceptions about carbohydrate metabolism and the function of glycogen in different organs have undergone a change. Muscle glycogen, previously considered to be of primary importance as an immediate source of energy for the contraction of muscle, has, according to present conceptions, at least the same significance for carbohydrate metabolism as liver glycogen.

A direct examination of the amount of glycogen present in the body in health and disease is not possible during life, our conceptions about

the changes of glycogen in different organs are based largely on the result of animal experiments. In man the formation and presence of glycogen, especially in the liver can only be investigated by indirect methods. Of these methods we may mention measurements of the blood sugar content in the fasting state and following the administration of carbohydrates, the changes in the respiratory quotient, the total metabolism, the blood sugar, the excretion of sugar in the urine, the lactic acid content of the blood, and the inorganic phosphate of blood and urine. In the clinical studies of the power of the liver to form glycogen, galactose and levulose are usually used. Recently these tests have been refined by studying concurrently the changes in the total blood sugar and in the levulose and the galactose of the blood. The presence of a ketosis is regarded as an indication that no glycogen reserve is present in the liver. The absence of a significant increase in the blood sugar content following the injection of adrenalin is also usually explained on this basis. The presence of a so-called initial *insulin-hyperglycemia* (not given by pure insulin preparations) has been regarded as proving the existence of a glycogen depot. In recent years several of these methods of investigation have been criticized, and their significance questioned. Thus it would seem that the changes in the respiratory quotient after the administration of different carbohydrates can no longer be explained in so simple a way as in the past. From the investigations of *Deuel*, *Cathcart* and *Markowitz*, *Campbell* and *Mallby*, and others, it appears in the first place that the respiratory quotient indicates the sum of different processes taking place at the same time, and is not merely an indicator for the simple fixation or oxidation of sugar. In the second place it appears that the divergent influence which different sugars have upon the respiratory quotient may be explained in this way, that certain sugars cause a rise of the lactic acid content of the blood, and secondary to this—by stimulation of the respiratory center—more carbonic acid is expired.

As regards the levulose tolerance test we know now that the possibility cannot be excluded that this sugar may be metabolized outside the liver (*Steinberg*, *Bollman* and *Mann*).

As to hyperglycemia occurring after injection of adrenalin, other factors besides a mobilization of liver glycogen, such as the trans

formation of lactate from muscles, must be considered, and also in the opinion of the Coris especially, a diminished assimilation of sugar in the tissues. The latter opinion is however still in debate (*Soskin, Priest* and *Schultz*). As to the significance of other hormones (insulin, thyroid hormone, adrenal cortex hormone and hormones of the anterior pituitary) and nervous influences for liver glycogen, recent investigations have partly changed several current conceptions and have taught us a number of important new facts.

Glycogen disease confronts us with a new condition, the possibilities of which as a means of throwing light on glycogen metabolism, have been only here and there appreciated. A glycogen depot exists in the liver, even an abnormally large one (eventually also the same is found in other organs), but this glycogen cannot be mobilized or only with great difficulty. Generally, it is considered impossible to obtain a true insight into the distribution of glycogen in the body by examination of the organs after death, because it is assumed that after death a more or less rapid decomposition of glycogen occurs. In glycogen disease, however, the organs after death are found to be loaded with glycogen, notwithstanding the fact that in some of these cases death has resulted from acute febrile disease, which as a rule causes rapid diminution of glycogen in the tissues.

Based on experiments with animals we know that the glycogen of the liver, especially, may vary greatly with the diet. A large glycogen supply in the liver can under normal conditions be as quickly broken down as built up, various factors such as the composition of the blood, hormones, the nervous system and also age may play a rôle in the process of glycogenesis. Under normal conditions the glycogen supply in the liver moves between definite limits. In animal experiments some investigators have succeeded in increasing the glycogen content of the liver greatly, and under certain circumstances this increase was accompanied by a marked increase in the volume of the liver. Further on we shall consider the possible significance of these experiments in the problem of glycogen disease.

The muscle glycogen is not changed so readily by variations in the food intake as is the liver glycogen (see *Hynd* and *Rother* and others). Between the carbohydrate metabolism of liver and muscle there is, however, a definite relation, known as the *Cori-circle*.

The glycogen of the heart muscle occupies a peculiar place, as it increases in the fasting condition and in other respects, too, behaves differently (see among others *Best* (1935) and *Yannet and Darrow*)

In diabetes mellitus, it was formerly assumed that the liver was poor in glycogen. Recent investigations, partly of experimental nature, have demonstrated, however, that even in diabetic coma the glycogen content of the liver may be about normal (*Major and Mann, Popper and Wosazek*). The glycogen content of the muscles in diabetes mellitus is normal. The presence of glycogen in the kidneys after death has been regarded as a more or less typical finding in diabetes mellitus.

The relationship between carbohydrate and phosphate metabolism has been clearly established from many recent investigations. Formation and solution of glycogen in the body can be judged by the changes occurring in the phosphate content of the blood after ingestion of sugars and injection of insulin on the one hand, and after injection of adrenalin, on the other. How far the results of these experimental studies can be applied clinically in following glycogenesis in the liver and in determining whether the glycogen there is mobilized with ease or difficulty, will be discussed later on.

As regards the relation between carbohydrate and fat metabolism it was generally accepted, until recently, that complete oxidation of fat was possible only when enough carbohydrate was available for combustion. Ketosis, therefore, was regarded as a symptom of incomplete fat combustion by a shortage of carbohydrate in the metabolic mixture. Recent observations have made it highly probable that this close relationship between fat and carbohydrate metabolism does not always exist. The metabolism of fat according to different investigators may be influenced independently by hormonal factors, originating especially from the pituitary gland. In discussing different symptoms observed in cases of glycogen disease, especially those in which the liver is principally involved, these new conceptions will have to be considered.

Of great importance for the problem of glycogen disease—especially since it is a disturbance manifesting itself mostly at or shortly after birth—is the conduct of the glycogen during fetal life. *Claude Bernard* found that glycogen was present in fetal tissues. Since

then, the investigations on glycogen during the embryonic period have been numerous. It has been repeatedly shown that glycogen accumulates in various embryonic tissues shortly before birth—it has been demonstrated particularly in the human liver—and it shows great stability. From the standpoint of function one of the differences between fetal glycogen and glycogen in the postnatal state is the fact that fetal glycogen cannot be mobilized in the cold and by adrenalin. In the normal new-born infant glycogen can often still be discovered in locations where in adults it is found only under pathological circumstances (in the kidneys and in organs of internal secretion). The glycogen of the new-born shows the interesting difference that relatively large quantities of adrenalin are required for its mobilization. These and many other facts demonstrate that pre-natal and neo-natal glycogen metabolism differ from that during the later years of life. The final cause of these and other peculiarities in glycogen metabolism has not yet been established with certainty. *A priori* we consider as possibilities hormonal factors, alterations in the behavior of the glycogen splitting ferments, and of the glycogen itself. We shall discuss these possibilities later on.

In the accumulation of glycogen of which we have been speaking, such as in the organs of the embryo and the new-born infant, or the pathological glycogen infiltration in diabetes mellitus, there has never been found an *enlargement* of the organ, caused by this glycogen accumulation, as occurs in glycogen disease. We prefer the name "glycogen disease" for this peculiar disturbance of glycogen metabolism, which has been described under various names (compare the literature at the end of this article), grouping the clinical types under the terms "hepatomegalia glycogenica", "cardiomegalia glycogenica," etc. We now propose to present a brief survey of the literature. In our discussion we shall pay attention principally to the *clinical* side of the problem.

2 HEPATOMEGALIA GLYCOGENICA

a Review of cases

Under the title "hepato-nephromegalia glycogenica" von Gierke published in 1929 the results of the autopsy of a girl, who died of influenza at the age of eight years and who probably since birth—at

least since the age of three and a half years—had shown a very large liver. Symptoms of lues or tuberculosis had not been observed during life. Whether the spleen was also enlarged remained doubtful. The girl repeatedly had epistaxis, showed rachitic symptoms, slight anemia and a tendency to infections of mouth and pharynx. In the urine were no pathological substances, in particular sugar was absent. At the age of five years the girl was too small for her age, the structure of bones was slender and the musculature was thin. The skin was normal.

At the autopsy, 24 hours after death, the length of the child appeared to be normal for her age. No ascites. *Von Gierke* found an enormously enlarged liver (weight 2000 gm, normal for this age about 740 gm). Both lobes of the liver, but especially the right one, were very much enlarged. Undoubtedly the enlarged left lobe, separated from the right one by a deep notch, had been mistaken for the spleen. The spleen itself was scarcely enlarged. The kidneys were, also, greatly enlarged (weight of both together 245 gm, normal about 130 gm). Adrenals and thymus were atrophic. The pancreas had a normal aspect, the islets of Langerhans were distinct. The histological examination showed that the enlargement of the liver was principally due to an enormous glycogen infiltration of the liver cells. Beside this, much fat was present in the liver cells. Also the enlargement of the kidneys was principally due to this glycogen accumulation. No glycogen infiltration or histological changes were found in the atrophic adrenals, in the spleen, spinal bone marrow, pancreas, thyroid, pituitary, ovaries, intestine and brain. Small pieces of the diaphragm and of the muscles of the neck, after being kept for fourteen days in formalin, contained only small amounts of glycogen. The results were the more curious as the patient died of an infectious disease and the organs could not be examined until 24 hours after death, which means that the organs were examined under circumstances where in the liver normally no glycogen or only a very small amount is found.

The chemical examination performed by *Schönheimer* confirmed these findings. Both liver and kidneys contained abnormally large amounts of glycogen. Even after being kept for six days at 37°C the glycogen content of the liver decreased very little. The autolysis

of the organs had in this case scarcely exerted any influence on the glycogen. *Schönheimer* found no indication for the presence of a peculiar kind of glycogen which could not be split in the normal way. He was of the opinion that the accumulation of glycogen *in vivo* and the disturbed postmortem destruction of glycogen in this disease was caused by the absence or shortage of liver amylase. Glycogen, isolated from the liver and the kidney, was rapidly broken down when mixed with normal liver.

Perhaps of interest from a clinical-diagnostic point of view we may mention the fact that *Schonheimer* was able to isolate a remarkable quantity of glycogen from the blood of the patient as late as six days after death. *Von Gierke* considered the possibility, mentioned by *Schönheimer*, that the condition represented a persistence of the fetal state, he agreed with *Schönheimer* that the process of glycogenolysis by enzymes was disturbed. The epithelium of the embryonal kidney supposedly would have only the property of building up glycogen and only later on would the glycogen-splitting ferments develop. Hepatomegalia in *von Gierke's* conception would be a kind of congenital disturbance of metabolism of liver and kidney cells, caused by a total or partial absence of glycogen splitting ferments. Therefore *von Gierke* spoke of a dysontogenetic "An- oder Hypenzymatose." Considering his case analogous to those diseases where there exists accumulation of metabolic products, as in *Gaucher's* disease (kerasine), and in the disease of *Niemann-Pick* (lipoids), *von Gierke* called the condition the "Glykogenspeicherkrankheit."

Von Gierke was also able to examine the organs of a second patient, a boy of five years, who since birth had had a very large abdomen. Blood and urine of this child had never been examined. Kidneys and liver were also greatly enlarged in this case and contained large amounts of glycogen. The liver showed in addition a slight increase of the periportal connective tissue. In the spleen, which was only moderately enlarged, no glycogen could be demonstrated.

These very important communications established the existence of a congenital disturbance in the glycogen metabolism, in which the glycogen can be mobilized only with great difficulty, and in which liver and kidneys are so engorged with glycogen as to bring about enormous enlargement of these organs. But, regardless of the im-

portance of the facts established by *von Gierke* and *Schönheimer*, they gave little help in regard to the recognition of these enlargements of organs by glycogen accumulation during life, as distinguished from other causes of hypertrophy of organs

For some years prior to the publications of *von Gierke* and *Schönheimer* we had been intensively occupied by the clinical and metabolic study of a boy who since birth had had a very large liver, and who clinically gave the impression of adiposo-genital dystrophy. One of the most important questions to which the examination of his metabolism led was whether the boy might have a glycogen depot in the liver, from which the glycogen could be mobilized only with difficulty, and whether this difficulty was related to the special disturbance in the carbohydrate metabolism which he showed

Our first case, a boy who is now sixteen years old, comes from a healthy family, *father and mother are own cousins*. He was born spontaneously at term. Soon after birth the mother's attention was drawn to the fact that the boy grew with extraordinary rapidity and that the abdomen grew larger and larger with marked development of the subcutaneous layer of fat. At the age of eight months the child came into the hospital for the first time, where a big abdominal tumor was diagnosed, either a large liver or a tumor adjoining the liver. The Pirquet, Wassermann and Weinberg reactions were negative. Normal blood picture. No hyperglycemia, no hypercholesterinemia.

At the age of one year and a half an exploratory laparotomy was performed. The liver was found to be enormous, smooth and apparently quite normal and had the aspect of a fatty liver, no biopsy was made. During the first years of life the child was admitted to the hospital on several occasions, but no exact diagnosis was made. During these years the boy showed noteworthy symptoms. He often suffered from attacks of vomiting, beginning without known cause and lasting for some days, at such times he gave the impression of being severely ill. We now think that these were attacks of periodic vomiting with acetonemia. Later on the relation between these attacks and the disturbance in the metabolism of the patient will be discussed. Furthermore the boy often had bloody stools, the blood could be seen macroscopically, and often was present in a rather large quantity. Occult blood could be repeatedly found in the stool. In the beginning we were of opinion that these hemorrhages were related to an obstruction in the portal system, caused by the tumor of the liver. Proctoscopic exam-

ination revealed that in addition to a hyperemic mucous membrane there was a rectal polyp, which undoubtedly was the principal cause of the rectal haemorrhages

In the beginning of 1927, at the age of five years, the boy came for the first time into the "Propaedeutic Clinic" At that time he was somewhat too small for his age but much too heavy, length 115 cm (normal 117), weight 26 kilos (normal 23) Extraordinary development of the subcutaneous fat layer was observed and a true paunch was present The external genitalia were small The thorax was normal There was a very large, hard, smooth liver, the lower border of which extended to the umbilicus The spleen could not be felt No ascites No polyuria In the urine, examined during the day, when the boy took the ordinary hospital diet, sugar could not be found, nor could urobilin No bile pigments were present but acetone was often found In fasting condition the urine nearly always contained much acetone and in addition a considerable quantity of β -oxy-butyric acid When taking a mixed diet the stools contained only traces of fat and very small quantities of carbohydrates Fundus oculi normal An X-ray of the skull showed an unchanged sella turcica, roentgenograms of the bones of the hand revealed a retardation in the development of the skeleton, which had been noted some years previously In Nov, 1927, only three or four of the bones of the wrist were present, whereas normally at this age they should nearly all be present In June, 1928, after a long period of ingestion of alternating thyroid and hypophysis preparations, the bones of the hand were still as underdeveloped as in Nov, 1927, the condition was unchanged in Dec, 1929, but in May, 1931, the skeleton of the hand was complete (see later on)

During the years in which the boy has been under our observation we have repeatedly examined the blood The haemoglobin content and number of the erythrocytes were always slightly diminished, the number of blood platelets was normal In Apr, 1928, the number of leucocytes was 4850 and later on also a distinct leucopenia was found, the leucocyte count at one time being 2900 The differential blood count repeatedly showed nothing remarkable, with the exception of a relative lymphocytosis and a slight eosinophilia Systolic blood pressure 105 mm The temperature was normal, no tendency towards a subnormal temperature was noticed — The mental development of the patient was quite normal for his age, he was and still is a bright boy, always gay and lively — In the beginning of his stay in the hospital he tired easily when walking or even when standing, but in this respect his condition ameliorated greatly

The urine of this boy in the fasting condition showed ketosis, and the

fasting blood sugar level was very low. Both findings, repeatedly confirmed, should, according to the conceptions current at that time, have excluded the existence of a glycogen depot. After ingestion of different carbohydrates there occurred a significant rise of the blood sugar level, although hyperglycemic values never were reached, sugar was never excreted in the urine, and the ketonuria could only be made to disappear with difficulty. The boy showed a striking preference for eating bread.—The changes, occurring in the respiratory quotient after ingestion of sugar, did not seem to point to a quick transformation of sugar into fat.—After adrenalin injection only a slight elevation of the blood sugar occurred, but the ketosis was considerably increased. The patient exhibited marked sensitiveness to a small amount of insulin.

From these findings and others to be discussed later on, we considered it highly probable that our patient was able to fix sugar in the form of glycogen and to an even greater degree than under normal conditions, notwithstanding the fact that in the fasting condition he showed a strong hypoglycemia and ketosis, symptoms which, according to the current conceptions, seemed to point to the absence of even a small glycogen depot. The result of the adrenalin experiment in particular, pointed to the fact that this glycogen depot could only be mobilized with difficulty. This conception was supported by the observations of *Wilder* and his co-workers on a patient with hyperinsulinism, adrenalin injection failed to produce any elevation of the blood sugar level, whereas after death the liver of the patient appeared to be full of glycogen. We attributed the anomalous disturbance which our patient showed to a continuation of the fetal condition and we sought an explanation of the condition in faulty glycogenolysis.

In our studies on the above mentioned patient we had profited in more than one respect by observations made on a somewhat similar child reported in 1921 from the Children's Clinic in Vienna by *Parnas* and *Wagner*. This child exhibited a hitherto undescribed disturbance in carbohydrate metabolism. This disturbance was manifested especially in the fact that in the fasting state no sugar or almost none could be demonstrated in the blood by the method in use at that time. In spite of the low blood sugar in this patient as in ours, also, those symptoms were lacking which we later on recognized as being

"hypoglycemic" in origin (the description of *Parnas* and *Wagner* dates from the time before insulin) Other particularities in their child's metabolism were that after ingestion of sugar or starch there appeared a hyperglycemia, accompanied by a marked glycosuria, both symptoms developing quickly Further, only slight elevation of the blood sugar content was found after injection of adrenalin Both the last-mentioned facts made *Parnas* and *Wagner* assume that in their case the liver was no longer able to form a glycogen depot out of sugar Furthermore the urine of the child described by them did not contain sugar in the fasting condition, but large amounts of acetone, diacetic acid and even β -oxybutyric acid, which substances quickly disappeared from the urine after the child had been given sugar or starch And clinically there existed symptoms demonstrating the existence of a complicated disturbance in the internal secretions Also the child was suffering from a very enlarged liver of firm consistency, without ascites and without tumor of the spleen

Partly from the fact that no sugar could be demonstrated in the urine of our patient after the ingestion of a large quantity of glucose, fructose or galactose (30–50 gm), and that none could be demonstrated when the very same quantity of sugar was repeatedly given at intervals of some hours (principle of *Staub-Traugott*), we formed the opinion that there existed an essential difference between the metabolism of our patient and the child of *Parnas* and *Wagner* Also the fact that after the ingestion of sugar there actually did appear a long continued bi-phasic curve, without, however, reaching real hyperglycemic values as in the case of *Parnas* and *Wagner*, pointed in our opinion to a difference between their patient and ours—When in later years we heard from *Wagner* that his patient had grown up as an ordinary diabetic, and that moreover the blood sugar content in the fasting state had significantly risen, whereas—a very remarkable fact—the tumor of the liver had become much smaller, then our opinion about the essential difference in the metabolism between both children was supported

After we had arrived at the probable conclusion that the explanation of the deviation in metabolism in our patient had to be sought in a faulty glycogenolysis, the publications of *von Gierke* and *Schönheimer* appeared The question then arose how far the symptoms found in our patient were characteristic of hepatomegalia glycogenica This

question was of great practical importance, since it necessitated the differential diagnosis (a), from other chronic liver diseases and (b), perhaps less important, from diseases of other organs (e g, adrenal and kidney tumors) It was also important, therefore, to decide whether a laparotomy should be performed

We continued the investigations in our boy and have been fortunate in being able to study (since 1932) the same conditions in a second child, a girl who, presented almost the same morbid picture with analogous deviations in the metabolism

Our second case, a girl now ten years old, was a full term child, delivered spontaneously Throughout her pregnancy the mother remained well The child's weight at birth was just over 7 lbs She was breast-fed until the age of ten months Her weight, when one year, was about 21 lbs Throughout this time the physical condition remained good and there was no evidence of rickets The mental development was normal There is much evidence to suggest that the child had a large liver at birth In a photograph, taken at the age of six months, the abnormally large circumference of the abdomen can be seen distinctly, and before the end of the first year the presence of an abnormally large liver had been established with certainty We know that during the first year of life no unusual incidents occurred

After the first year of life this child, just as in the case of our first patient, had periodic attacks of persistent vomiting in the morning and showed also a special preference for bread When the mother came to us with the child in January, 1932, there were no other complaints apart from this nausea and vomiting The child was hindered in her movements by the enormous abdomen She was alert, the mental development was normal, and she attended a preparatory school She had a good appetite, had no abdominal complaints and no attacks of fever

The father was healthy, the mother was 37 years old when the child was born, this being the seventh pregnancy and the child the first of her second marriage She had had one abortion and a still born twin One child died at the age of one year from bronchopneumonia following measles The other children were normal There was no known enlargement of the liver in the family Of the medical condition of the first husband little is known, except that he was a drunkard The Wasserman reaction (Jan. 1932) of the mother was negative Since the birth of her girl the mother has had no further pregnancies No family history of ~~tuberculosis~~

On examination (Jan , 1932) the girl, nearly five years old, weighed 35½ lbs , and was only 38 in in height She was well nourished with normal subcutaneous fat, and no suggestion of adiposity No icterus The skin was somewhat dark in color, there was no pigmentation of skin or mucous membranes No abnormal growth of hair Rather marked dental caries The neck was short, and on both sides were numerous small glands The abdomen was protuberant Heart, blood pressure and lungs were normal

The abdomen was greatly but evenly distended, and on the upper part of the wall of the abdomen a fine network of veins was seen, no caput Medusae The distension of the abdomen was caused by a very large liver, which occupied nearly the whole right and the greater part of the left half On the right side it was almost impossible to place the hand between the liver and the edge of the pelvis The left lobe could be felt from the level of the umbilicus, slanting upwards and disappearing under the costal arch at about the axillary line Just at the umbilicus an incisura could be felt. The liver was of firm consistency and smooth, its edge was sharp No pain on palpation of the abdomen, no signs of free fluid The greatest circumference of the chest was 21 in and of the abdomen 25 in The spleen could be felt with difficulty, kidneys were not palpable External genitals normal Reflexes normal Muscular system normal The legs were slim The child was not easily exhausted by exercise

The girl was intellectually normal for her age She complained of no abdominal symptoms, and showed no clubbing of the fingers

The urine obtained while fasting contained no albumen or sugar, and showed a weakly positive reaction for urobilin, and strongly positive tests for acetone and diacetic acid Bile absent Specific gravity normal Nothing abnormal in the sediment Stool normal color and consistency, no worms or ova, on a mixed diet the fat and carbohydrate content was not increased The Pirquet, Wassermann and Weinberg reactions were all negative Temperature normal

Examination of the blood showed a leucocyte count of 12,700 with 5 per cent eosinophiles and a moderate relative lymphocytosis, no anemia, platelets normal The blood was investigated repeatedly with similar results except that in later examination the leucocyte count was normal and the eosinophilia less A distinct leucopenia, as found in the boy, was not encountered

X-ray investigation showed no enlargement of the heart, no signs of active rickets, no apparent abnormalities in the extremities with the exception of several small transverse lines in the bones of the legs denoting

irregular growth There was some delayed ossification, in both wrists only three of the carpal bones were ossified Sella turcica normal Kidneys normal, no abnormalities in the region of the adrenal glands Bones of the skull were normal

Electrocardiogram normal Basal metabolism slightly increased (two determinations, + 19 and + 27 per cent. At the second determination the child was not quiet)

The girl, therefore, showed a greatly enlarged liver without demonstrable hypertrophy of other organs, but with definitely delayed growth Marked ketosis and slight urobilinuria were present No signs of an endocrine disturbance were found and especially no marked adiposity as was found in our boy

Blood sugar In the fasting condition there was a combination of hypoglycemia and ketosis in the capillary blood the sugar at different determinations ranged between 0.046 and 0.059 per cent, in the venous blood between 0.05 and 0.06 per cent (Hagedorn and Jensen) All clinical symptoms of the so-called hypoglycemic complex as occurs in hyperinsulinism were absent.—In addition, after 25 gms of glucose, there was a biphasic blood sugar curve The blood sugar remained increased for a long time and had not returned to the fasting level after 2½ hours, which in itself is strongly against hyperinsulinism The maximal elevation was only from 0.058 to 0.112 per cent, no glycosuria occurred

After 20 gm of levulose the fasting blood sugar rose from 0.056 to a maximum of 0.088 per cent, i e., a little higher than may occur normally (30 mgm per cent), but the increase lasted for more than two hours The urine contained no reducing substances, and the ketosis present in the fasting condition decreased very much after giving levulose.

After 25 gm of galactose no sugar was excreted in the urine.

The elevation of the respiratory quotient after giving 20 gm of glucose was investigated, in one hour the quotient rose above 1, but the girl did not remain quiet

Adrenalin test After subcutaneous injection of 0.5 mgm of adrenalin the girl showed only a very slight elevation of the blood sugar in the first test from 0.054 to 0.07 per cent, in the second test from 0.051 to 0.066 per cent. But a marked increased excretion of ketones after the adrenalin injection was noticed

Our idea of the cause of the blood sugar elevation after adrenalin injection in 1933 had to be considered The *Coris* had demonstrated in different ways that the blood sugar elevation which normally occurs after adrenalin injection is only partly caused by mobilization of liver glycogen and this

only in so far as the primary elevation is concerned. In speculating as to the existence of a glycogen depot in the liver which can be mobilized, stress must therefore, *a priori*, be laid upon the non-appearance of this initial elevation. In both our patients, however, it appeared that the adrenalin effect was also abnormal in so far as the rise in the lactic acid content of the blood, which normally accompanies adrenalin hyperglycemia and which is related to an increased splitting of muscle glycogen, was only very slight.

In this connection we wish to point to the disturbance of glycogen splitting and of lactic acid formation in muscle, which occurs after extirpation of the adrenals and is accompanied by an increased consumption of creatine-phosphoric acid (see among others *Kuschinsky* and *Nachmansohn*). It appeared that creatine was present in the urine of both our children, but in a normal amount for their age.

In still another way the adrenalin effect in both our children appeared to deviate from the normal. When in normal men subcutaneous injection of adrenalin is combined with oral administration of glucose in the amount normally used for tolerance tests, then the elevation of the blood sugar is for the most part much more marked than would be expected from an addition of the effect of adrenalin and of glucose ingestion (*Burkens*). This is apparently a consequence of the second adrenalin effect (the *Coris*), that is, a decrease of sugar consumption in the muscles as a result of which the extra glucose given orally causes a higher elevation of the blood sugar. In both our patients such a test was carried out once. In both cases the elevation of the blood sugar after adrenalin injection together with glucose ingestion was only slightly greater than after glucose ingestion alone.

From an investigation of the protein of the blood serum it appeared that the significant increase of the globulin content of the serum, which is present in the majority of chronic parenchymatous liver affections (*Bendien* and *Snapper*) was absent in both our patients.

With the serum of both patients we performed the flocculation test which, according to recent investigations, is always positive in chronic parenchymatous liver affections when the globulin content is distinctly increased, (the so-called Takata-Ara-reaction). In our boy the test was negative, in the girl it was only weakly positive.

Corresponding to normal values obtained for the proteins of the serum, the sedimentation rate of the erythrocytes in the defibrinated blood as well as in the non-defibrinated blood of both our patients was normal (*Bendien* and *Snapper*).

Certain determinations of different constituents of blood and blood serum have also been made in both our patients. From these it appeared

that in the girl as well as in the boy there was a marked elevation of the cholesterol content. In both our patients the relation between free cholesterol and cholesterol esters, a relation which in liver diseases is often changed, was normal. There was no decrease of cholesterol esters. In both our patients with hypoglycemia the non-sugar reducing fraction and glutathione content were normal. It further appeared that the lipolytic activity of the serum of both our patients was also normal. In addition, a quinine- and an atoxyl-resistant lipase (as may be present in the serum in parenchymatous liver and pancreas affections) were absent from the serum.

We studied in different ways the glycogen metabolism of both our patients, firstly, the so-called initial insulin hyperglycemia which, when present, would prove the existence of a glycogen depot. The effect is not given by pure insulin preparations. Using an insulin preparation of Burroughs, Wellcome & Co., which in animal experiments was proved to produce an initial rise in blood sugar, we found no such effect in our girl. The absence of this effect in her case is, as we now know, not due to an insufficient glycogen depot, but to a glycogen supply which can be mobilized only with difficulty. The glycolysis of the blood of the girl was normal, as was that of our boy. The same holds true for the influence exerted by insulin *in vitro* on the oxidative glucose fermentation by erythrocytes of our patients.

The quantity of diastase in blood and urine of both patients proved to be normal. Again, the so-called diastase-fortifying action of the blood serum, by which is meant the smallest quantity of serum which *in vitro* exercises a fortifying action on a pancreatic amylase, was normal in both our patients.

Special attention was paid to the glycogen in the blood of our patients. Could this glycogen be split? Little was known regarding the glycogen of the blood in general. According to *Gabbe*, in the normal blood the glycogen should, even on keeping for several hours at 37°C, decrease only very slightly, notwithstanding the presence of a glycolytic ferment. Thus the blood glycogen should in its degree of stability resemble the glycogen present during fetal life. It should differ in this respect from that normally present in liver and muscles, but correspond to that existing in liver and different organs in glycogen disease. With our method, described in 1934, which could be regarded as a micro-modification of *Pfäffer's* method, we had obtained for the glycogen content of the blood of the boy in the fasting condition some results which could be called distinctly high. Since then we have constantly found in the fasting blood of both our patients values which we look upon as high, no leucocytosis being present which could cause this elevation. Glycogen content of the blood (as mgm per cent of glu-

cose) case 1 (boy) 26, 25, 23.05, 27.5, 22.9, 26.62, 26.25, 24, 28, 25, mean value 25.43 Case 2 (girl) 23.75, 23, 20, 19.25, 21.25, 18.75, 21.35, 21, mean value 21.04 It appeared that the increase was principally caused by an increase of the glycogen in the blood cells —In children under 12 years of age, with the exception of our patients, we found by our method only two glycogen values above 20 mgm per cent (in a premature child and in a child with miliary tuberculosis), as a rule the values were much lower and corresponded to those recently obtained by *Staub* and *Golandas* On these grounds we thought we were justified provisionally in saying that the elevation of the glycogen content of the blood was of some diagnostic value in the diagnosis of hepatomegalia glycogenica We said "provisionally" because blood of infants with other forms of liver hypertrophy was not available In adults with liver hypertrophy values such as those found in both of our children also occur When the number of leucocytes is greatly increased, this in itself may be the explanation of a marked elevation of the glycogen content In an adult female patient with myeloid leukemia and a large liver (150 000 leucocytes) we found a very high glycogen content of the blood in two determinations, 48.5 and 71 mgm per cent, expressed as glucose

As to the splitting of the glycogen of the blood we agreed with *Gabbe* in judging that this glycogen could be split only with difficulty Blood was collected with aseptic precautions and received in sterile tubes After incubation for $1\frac{1}{2}$ hours at 37°C the blood of our patients showed no splitting of its glycogen In normal children the blood glycogen not uncommonly showed marked splitting in the same time —In keeping the blood for 48 hours at 37°C we constantly found a definite but varying decrease of the glycogen content of normal blood In our patients the decrease of the glycogen content of the blood under the same conditions which are so favorable for splitting, proved to be smaller than the mean decrease in the control patients and it scarcely agreed with the lowest values found in control children Further, we found that glycogen added to the serum of our patients and to the serum of control patients was split by both in the same degree and in the same time These experiments may indicate that in our patients the glycogen in some way or another was more protected against splitting than in the control patients

Our next step was to find out whether by mixing the blood of our patients with that of control children and keeping it for 48 hours at 37°C , the splitting of the blood glycogen of our patients could be accelerated Increased glycogenolysis was not constantly found, however, so that we were not justified in concluding, as we thought at first, that there existed

in normal blood a substance which favored the splitting of the blood glycogen of our patients

We did not think we were justified, when we knew so much about the metabolism of our children, in having a laparotomy performed and a biopsy made of the liver in our second case. We tried to demonstrate the presence of much glycogen in available cells. However, in this second case, in epithelial cells (mucous membrane of the cheek, cells of the pelvis of the kidney in the sediment of freshly voided urine) we could demonstrate no glycogen by the staining method of *Best*, nor could we find an increased amount of glycogen in the urine. In the leucocytes from a small granuloma at the root of a molar we found much glycogen. This in itself certainly had no great significance, but the absence of glycogen in this tissue would not have been in keeping with the morbid picture.

In summarizing the above results of the clinico-chemical investigation, we found in both of our cases

- 1 A combination of hypoglycemia and ketosis in the fasting condition
- 2 An abnormal adrenalin effect, expressing itself by
 - a Absence of a distinct elevation of the blood sugar
 - b A marked increase of the ketosis
 - c. Only a small elevation of the lactic acid content of the blood
- 3 An abnormal blood sugar curve after ingestion of glucose, unaccompanied by glycosuria
- 4 No diminution in tolerance to galactose and fructose
- 5 Absence of the so-called initial insulin hyperglycemia
- 6 Normal values for the diastase activity of blood and urine and normal diastase activating effect of the serum
- 7 Increased glycogen content of the blood, which could not be explained by leucocytosis
- 8 Normal glycogen splitting activity of the blood serum
- 9 Decreased glycogenolysis of the blood glycogen in incubation for two days at 37°C, compared with control cases
- 10 Normal protein partition in the blood plasma, especially no increase of the globulin content
- 11 Hypercholesterolemia with normal relation between free cholesterol and cholesterol esters

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Our conception that the disturbances in metabolism in our cases were more or less typical for glycogen liver, then was strengthened in our opinion by the description of cases from other sources. Before going into the details of these cases of hepatomegalia glycogenica which have been described in recent years, the following facts must be noted. In glycogen disease we are dealing not only with an abnormal accumulation of glycogen in the *liver*, but in other organs as well. *Von Gierke* has observed an accumulation in the kidneys, organs in which the glycogen is found only under exceptional conditions (especially in diabetes mellitus, and in the fetus and new-born infant). However, it has been established with certainty from more recent investigations that in cases of glycogen disease, an increased glycogen content could be found in nearly all the organs examined at autopsy. But only in certain organs was this finding accompanied by any considerable enlargement. These organs showing enlargement were in some of the cases liver and kidneys together, as in the first cases reported by *von Gierke*. In the majority of the cases the liver was pathologically enlarged, whereas the kidneys were of normal size. Next to this there have been described a number of cases in which the glycogen accumulation, combined with considerable enlargement of the organs, concerned especially the heart and in a few cases also other organs. This enlargement of other organs than the liver, caused by accumulation of glycogen, will be discussed in separate chapters.

Are the deviations from the normal metabolism, found in cases of hepatomegalia glycogenica, typical for this disease? Properly speaking, we should be influenced only by the alterations found in those cases in which the diagnosis of glycogen-liver has been confirmed by autopsy or by a biopsy of the liver during life. Indeed there is a limited number of cases which satisfy these requirements. The alterations found in those cases were for the greater part and in a high degree analogous to those which we had already established in both our patients.

Most of the cases of *hepatomegalia glycogenica* give a similar history. Rarely directly after birth, often during the first months of life or sometimes even later, an enlargement of the circumference of the abdomen to a more or less considerable degree is established. A large liver can be felt and one has to think of a disease of the liver itself, or of a

tumor, at this age especially of the adrenals, with metastases in the liver. Often an enlargement of the left lobe of the liver is taken for a spleen. If then, as not rarely happens, an exploratory laparotomy is performed, generally an enlarged liver is found, normal in color and consistency. The enlargement as a rule is extraordinary, the left lobe of the liver often appears to reach far into the left hypochondrium. The combination of a large liver and erroneously diagnosed large spleen has often given rise to various diagnoses. The following observation of *Bellingham Smith* and *O'Flynn* is of interest in this respect, but also from another point of view.

On Feb 16, 1931 a boy of six years was admitted into the hospital for coughing, breathlessness and abdominal pains. The mother had first noticed some enlargement of the abdomen at the age of fifteen months. He was demonstrated in 1931 as a case of *Gaucher's* disease. This last diagnosis was based on tissue pulp, containing large clear cells, from what was thought to be a splenic puncture, but which in reality was got by puncture of an enormously enlarged left lobe of the liver. The child showed a clinical picture that is seen in many cases of hepatomegalia glycogenica: it was too small for its age, the head was abnormally large, the face was fat and flabby. The abdomen protruded to a considerable degree, while the rest of the trunk and limbs were poorly covered. The muscular development of the lower limbs was particularly poor. The boy showed a very marked pigmentation all over the body and a profuse, abnormal growth of hair. The mental development was considerably retarded. The liver was greatly enlarged. Death on Dec. 27, 1931.—At the autopsy, weight of the liver 2500 gm, spleen 75 gm. Kidneys slightly enlarged. Suprarenals and pancreas normal. The liver was smooth, firm, pale buff in color, consistency of hard rubber, cut surface was smooth, homogeneous, very dense and somewhat translucent.

Sections of the liver stained by hematoxylin and *van Gieson's* stain showed under the high power vacuole formation in the liver cells which were increased in size, preservation of the nucleus in most cells and increase in connective tissue. The substance in the liver cells consisted of some material which was neither fat nor lipoid and was not doubly refractile.—The clinical diagnosis of *Gaucher's* disease previously arrived at, had to be rejected.—*Sections stained for glycogen were negative*.

An inquiry into the family history showed that one of the other children, a girl, also had a very enlarged liver, and died of terminal pneumonia at

the age of twenty months At the post-mortem the spleen was only slightly enlarged, the liver was enormous, weighing 1190.5 gm The liver was described as having no typical parenchyma and being in a state of extreme fatty degeneration —The authors are strongly inclined to accept that in their case the enlargement was due to glycogen storage, as in *von Gierke's* case The fact that they were unable to demonstrate glycogen in their case is ascribed to the fixative used

Certainly in this case we had to do with 1 a hepatomegalia of familial character, accompanied by 2 heavy pigmentation, and abnormal growth of hair on the body Furthermore, during life with the methods applied no signs of liver insufficiency could be found Extraordinary enlargement of the liver, peculiar color and consistency, the appearance of its cut surface and a peculiar appearance of the liver cells themselves on microscopic examination were features The large inflated cells of the liver showed a surprising resemblance to those found in cases of irrefutable hepatomegalia glycogenica We were able to convince ourselves of this fact by the examination of a section of the liver presented to us by Dr *O'Flynn* Whether we had to deal here with a familial hepatomegalia glycogenica is very uncertain, the more so since in the deceased sister extreme fatty degeneration of the liver had been found This point will be discussed later on

Of those cases of glycogen disease in which the diagnosis during life has been confirmed by biopsy of the liver, we shall mention first the one of *Beumer* and *Loeschke* They studied a child with a disturbance of the carbohydrate metabolism analogous to that in our first patient

The patient reported by *Beumer* and *Loeschke* was a boy of three years of luetic parents The mental and bodily development was essentially normal After the first year of life the abdomen became more and more distended, the diagnosis of luetic hepato-splenomegaly was made In vain the boy was treated with stovarsol and bismogenol At the exploratory laparotomy at the age of three years the boy appeared to have an enormous, smooth liver Both lobes were separated by a deep fissure The liver extended on both sides to the border of the pelvis —Examination by *Putschar* of the small piece of liver removed at operation showed a uniform and marked accumulation of glycogen in all the liver cells (*Best-stain*) The cells as a result of their increased size greatly resembled plant cells

Clinically this child now and then suffered from attacks of deepened respiration and distinct hunger for carbohydrates. The examination of the metabolism demonstrated that there existed

1 Acetonuria, which did not disappear when the child took the usual meals for children of his age, with hypoglycemic values in the fasting condition ranging from about 50 to nearly 70-90 mgm per cent, the normal values

2 After the ingestion of 40 mgm of glucose a long lasting hyperglycemia without glycosuria and without the disappearance of the acetonuria. The tolerance for galactose was at the level of 30 gm. The stronger anti ketogenic effect of galactose in comparison to glucose could be inferred in this case from the disappearance of the acetonuria

3 After the injection of adrenalin only a minimal elevation of the blood sugar content. Adrenalin injected subcutaneously together with 20 gm of glucose administered orally at the same time, gave an increased acetonuria and no glycosuria as normally. Excessive sensitiveness to insulin

4 Moderately increased glycogen content of the blood, which perhaps could be explained by leucocytosis (24,800 white cells of which 86 per cent were leucocytes)

5 Diastase of the blood serum slightly decreased, that of the 24 hours urine greatly increased

For the most part these results are similar to those we found in both our patients. The authors carried out a test with a fat meal in their case, the result of which was thought to be of diagnostic significance. We shall refer to this test later on.

The results of the experiments with adrenalin and insulin led the authors to conclude that it was uncertain whether the accumulation of glycogen and the inability to mobilize it were connected with a hyper- or hypoproduction of one of the two hormones concerned. They could not give an explanation for the abnormally large excretion of diastase in the urine.

Shortly after the publication of *Beumer* and *Loeschke* there appeared the communication of *Schall* on three cases of hepatomegalia glycogenica. In one of these three cases (the girl) an exploratory laparotomy was performed and a small piece of liver was removed for closer examination.

The children reported by *Schall* were, respectively, eight and one-half years old (girl), fourteen months old and four years old (both boys), when they were examined for the first time. In all three cases investigation of the family was unsuccessful. At birth the children did not have any peculiarity. The first abnormality to strike the attention of the parents was the increase in the circumference of the abdomen, this was observed in the second patient as early as the fourth week of life. This child was very delicate, whereas the other two children were strong, even strikingly big children. All three were late in learning to stand and to walk.

In the first and third patient an increasing adiposity developed, especially in the first, which suggested a disturbance of the internal secretions. In all three the mental development was normal. Two showed a definite disposition to infections.

Schall draws special attention to the typical external habitus in his own cases: marked adiposity with a distribution of fat differing from that found in dystrophia adiposo-genitalis. Clinically no evidence was found for a hypophyseal disturbance, nor in the girl was there indication of any dysfunction of the thyroid gland or ovary. The skeleton was slender and delicate in structure. The ossification in all three cases showed retardation which was, however, within the physiological limits. The musculature was moderately developed, especially in the first two cases and the tonus was decreased.—All three children showed a marked retardation of growth in stature, especially the girl who in addition was much too heavy. In none of the cases was the heart enlarged.—In all three children the liver was greatly enlarged. The skin of the abdomen displayed the pattern of the veins without a pronounced caput Medusae. The surface of the liver was smooth. The organ itself was not particularly firm or hard, not painful when pressed, and showed no pulsation. In the girl the notch was definitely to the left of the umbilicus. At the exploratory laparotomy on the girl the liver was found to have a smooth, glossy surface and was red in color, perhaps somewhat more red than normal. Histological examination of the piece of liver, which on removal was immediately fixed in alcohol, demonstrated a swelling of the liver cells with glycogen, with some affection, also, of the nuclei. In a small piece of *muscle* which was removed at the same time, *no glycogen was found*.

The blood picture did not show any abnormality, in particular there was no leucocytosis or relative lymphocytosis. The blood serum was normal in color. No glycogen could be demonstrated in the blood.—The Mantoux-reaction was positive only in the first patient and then only feebly so, but the child did not show clinical indications of tuberculosis. Sugar was never found in the urine.

In the first case there was nearly always *acetonuria* and excretion of diacetic acid while the patient was fasting. Two to three hours after the first meal the ketonuria disappeared. In the second case *acetonuria* was present only during the period of fever. In the third case *acetonuria* occurred occasionally during a fast and after food had been taken but very inconstantly. An explanation for this variation could not be found.

In all three cases of *Schall* a hypoglycemia existed, the lowest values found in the three cases were 24, 25 and 19.5 mgm per cent respectively. At the time when those low values existed in the blood there were no clinical symptoms of hypoglycemia, as occur in hyperinsulinism.

The blood sugar curve after the tolerance test with glucose was abnormal in all three cases: a more or less quick elevation was followed by a retarded decrease, while the level at the beginning of the test was not reached even after three to four hours. Also, after the tolerance test with other sugars and with starch a retarded curve was obtained. Repeated ingestion of sugar according to the *Staub-Traugott* method gave an abnormal result, i.e., no flattening of the blood sugar curve after the second, and especially after the third ingestion of sugar, but an abnormally high curve with an elevation which lasted for three hours.

In all three cases injection of adrenalin, though having a distinct effect on the circulation, did not produce any effect on the blood sugar level.

In the eldest child, the girl, the basal metabolism was found to be increased, +33 and +16%, respectively, in two determinations. The respiratory quotient after the tolerance test with glucose was increased, after two hours and after four hours it was still found to be increased, its value did not rise higher than unity, however.

The adiposity, characteristic in some of the children, could be explained according to *Schall* on the basis that as the glycogen-depots are overfilled, fat is formed from the sugar of the food. An argument for this hypothesis is perhaps found in the late elevation of the respiratory quotient after the ingestion of glucose.

In accordance with the findings of *Schönheimer*, *Schall* is of the opinion that perhaps a failure or disturbance of the function of the diastase of the liver is the principal cause of the morbid picture.

At about the same time as *Schall*, *Unshelm* described two cases in two brothers. Moreover, the author in a later publication stated that both grandmothers of the patients were cousins.

Both children died in the second year of life. The mother of the first child, when the latter was five months old, had the impression that he was very delicate, at the age of one year growth was greatly retarded, and the child was still unable to stand. From birth the abdomen must have been very distended and this distension had increased during the last months before the child was taken into the hospital. When about one and one half years old convulsions occurred. When twenty months old the child had full red cheeks and the whole body was covered with lanugo hairs. There was a sufficient layer of fat, the muscles were soft, the turgor was good. The abdomen was enormous, the liver palpable, hard and smooth, spleen not enlarged. Exploratory laparotomy was performed, the liver proved to be greatly enlarged, liver puncture gave no results. Three weeks later the child died. No autopsy. Nothing is stated with regard to blood or urine.

The other child was born with a very large liver (birth weight 4750 gm). Three weeks after birth increasing distension of the abdomen was noted. At the age of fourteen months the layer of fat and the muscles were moderately developed and soft. The liver occupied nearly the whole abdomen. At the age of twenty months the possibility of a familial glycogen disease was considered for the first time. The boy was then greatly retarded in height and weight, looked much younger than his age, but had red and full cheeks with ectasias of the veins. Abdomen and liver were enormous, the lower extremities were remarkably thin. There was fine lanugo on the upper part of the trunk. The child was unable to sit upright unaided. In the fasting condition the expired air had the odor of acetone. Shortly after this examination hyperpyrexia developed and death occurred after a week's stay in the hospital.

Röntgenologic examination during life had demonstrated a marked osteoporosis with the characteristic symptoms of irregular growth. Development of the nuclei of the bones was greatly retarded. The urine in the fasting condition showed almost no reduction. After food had been taken a weak reduction was noted and a slight ketonuria. Strikingly large amounts of diastase were demonstrable in the urine. This diastase appeared to be able to split starch as well as glycogen.—There was moderate anemia and slight leucocytosis with relative lymphocytosis. The diastatic ferment in the blood was not absent.

At autopsy (performed by *Kimmelstiel*) the heart did not appear to be enlarged (weight 50 gm). The liver weighed 1600 gm, the kidneys each weighed 45 gm. The adrenals were somewhat smaller than normal. On histological examination the interlobular connective tissue in the liver

proved to be definitely increased, in addition there was present a moderate fatty infiltration of the liver cells. The protoplasm of these cells was very rich in glycogen. The kidneys contained less glycogen than the liver but large amounts of it were found in the lymph spaces and in the fibers of the *heart muscle*, in the lymph spaces and in the sarcolemma of various *striated muscles*, and in different parts of the *brain*. The distribution of glycogen, therefore, was very peculiar in this case.—In the pancreas some enlarged islets were present alongside many normal ones. In the organs of internal secretion no glycogen was found.—When examined seven days after death the glycogen content of the viscera appeared to be about the same as previously. In the liver the amount of glycogen present was found to be 14.2% (moist weight), which was more than *Schönheimer* could find in the case of *von Gierke* (10.43%).

Both *Schönheimer* and *Unshelm* carried out detailed studies with reference to the cause of the stability of the glycogen. As has been mentioned before, *von Gierke* and *Schönheimer* had concluded, especially from the autolysis experiments, that the accumulation of glycogen *in vivo* (in liver and kidneys) and the disturbed postmortem destruction of the liver glycogen in glycogen disease was caused by the absence of the diastatic ferment in the liver. The glycogen isolated from the liver proved to be converted normally when amylase was added. This conception seemed to conflict with the experience of some investigators who found that in the blood and urine of patients with glycogen disease the diastase is present in normal or even in increased quantity. *Unshelm* was able to find, furthermore, that starch added to the pulp of liver in his case was converted in a normal way, so the liver itself apparently contained a sufficient quantity of active diastase ferment. Conversely, when he added intact liver to the minced liver in his case, the glycogen was quickly destroyed. Thus one had to assume that, on the one hand, there was present active diastase ferment in the blood and in the liver, and, on the other hand, that the (accumulated) glycogen could be split. If this *in vivo* and postmortem destruction of glycogen in the glycogen liver (and in some other organs) could be performed only with difficulty, then this peculiarity might be explained, according to *Unshelm*, by the fact that in this disease the glycogen is protected against glycogenolysis in some peculiar way. He thought, more especially, of an abnormally strong

adsorption or chemical fixation of glycogen to protein, which might be loosened relatively easily

The pathologist, *Kimmelstiel*, who performed the autopsy in this case also reported some interesting researches on the nature of the disease. Based on the results of these he saw the cause of the failure of the glycogen to be destroyed in the glycogen itself. In glycogen disease the blood sugar may already be heterotypical and the glycogen formed from it by polymerisation should have a structure deviating from the normal. This should bring about a very retarded destruction of glycogen in the liver by fermentation. Even if the destruction took place in a normal way, the glycogen must accumulate to a high degree. *Kimmelstiel*, for instance, found that glycogen from the glycogen liver gave, when destroyed by means of diastase, a product which was 25–28 per cent smaller than that which could be obtained from glycogen from another source (dogs, glycogen of *Kahlbaum*).

Faber was also able to perform an autopsy on a child with glycogen disease, a girl who died at the age of twenty-seven days.

The child was born somewhat prematurely, and weighed 2300 gm. Directly after birth the very distended and firm abdomen was a prominent feature. From the third day of life on, the baby suffered at intervals from diarrhoea, shortly before death it had fever and suffocating cough. At autopsy "hepato-nephro-megalia glycogenica" was found, as in the cases of *von Gierke*. The autopsy was performed twenty-eight hours after death. — The weight of the liver was 425 gm, of the left kidney 25 gm, of the right 23 gm. In the liver the glycogen was found to be 15.3% by moist weight, in the kidneys 5.9%. The pancreas furthermore contained only a few islets of Langerhans, which, as in the case of *Unshelm-Kimmelstiel*, had partially undergone pathological change, viz abnormal enlargement. Along with this were also found signs of pancreatitis.

Together with *Vendég*, *Faber* performed some experiments with the glycogen isolated from the liver of this child, in order to control the above mentioned hypothesis and experiments of *Kimmelstiel*. The behavior of this glycogen, however, with regard to its fermentative destruction with diastase preparations, as well as its complete destruction by boiling with diluted HCl, did not differ from that of glycogen preparations which had been prepared in other ways. Thus the

hypothesis of *Kimmelstiel* with regard to the pathological nature of the glycogen in glycogen disease could not be confirmed

Lindsay, Ross and Wigglesworth recently described a case in a French Canadian boy

When seven months old the boy began to vomit, and his abdomen was noticed to be unduly large. He kept on with frequent attacks of vomiting and his abdomen continued to enlarge slowly. At the age of 27 months the child was rather short and gave the impression of being very fat. The nutrition of the arms and legs was, however, poor, muscles were soft and flabby. Mentally he was very placid and coöperative—Systolic murmur at the apex of the heart. Heart not enlarged. Dilated superficial veins over the upper part of the abdomen. Surface of the enormously enlarged liver smooth and firm. Genitalia normal.

Hypoglycemia in the fasting condition, ranging from 20 to 37 mgm per cent—Low sugar tolerance curve, no glycosuria, no acetonuria. No rise in blood lactic acid after injection of adrenalin, but slight acetonuria. Lipemia and high blood cholesterol. Tests with sugars for liver function gave normal figures. The biochemical findings closely corresponded to those found in our two patients.

Biopsy of the liver was done. Chemical analysis of a section of the liver revealed three times the normal amount of glycogen and only one-third of the amount of fat usually found. Microscopic sections stained for glycogen gave the typical appearance found in glycogen liver. Furthermore, *signs of an early cirrhosis of the portal type were found*. The boy exhibited a definite penchant for potatoes and bread, and was unable to walk without assistance. The patient died shortly afterwards from a rapidly progressive pneumonia. At the autopsy the liver was found to weigh 2150 gm, i.e., about four times the normal weight at this age. The spleen was slightly enlarged, the heart, kidneys and endocrine glands were not grossly affected.

We now proceed to describe the more recently published cases of glycogen liver. In the majority autopsy or biopsy confirmation is lacking but it was furnished in the three cases of Krakower, the second case of Harnapp and the recently case of von Gierke.

Exchaquet in 1931 described three members of one family—older

adsorption or chemical fixation of glycogen to protein, which might be loosened relatively easily

The pathologist, *Kimmelstiel*, who performed the autopsy in this case also reported some interesting researches on the nature of the disease. Based on the results of these he saw the cause of the failure of the glycogen to be destroyed in the glycogen itself. In glycogen disease the blood sugar may already be heterotypical and the glycogen formed from it by polymerisation should have a structure deviating from the normal. This should bring about a very retarded destruction of glycogen in the liver by fermentation. Even if the destruction took place in a normal way, the glycogen must accumulate to a high degree. *Kimmelstiel*, for instance, found that glycogen from the glycogen liver gave, when destroyed by means of diastase, a product which was 25–28 per cent smaller than that which could be obtained from glycogen from another source (dogs, glycogen of *Kahlbaum*).

Faber was also able to perform an autopsy on a child with glycogen disease, a girl who died at the age of twenty-seven days.

The child was born somewhat prematurely, and weighed 2300 gm. Directly after birth the very distended and firm abdomen was a prominent feature. From the third day of life on, the baby suffered at intervals from diarrhoea, shortly before death it had fever and suffocating cough. At autopsy "hepato-nephro-megalia glycogenica" was found, as in the cases of *von Gierke*. The autopsy was performed twenty-eight hours after death. — The weight of the liver was 425 gm, of the left kidney 25 gm, of the right 23 gm. In the liver the glycogen was found to be 15.3% by moist weight, in the kidneys 5.9%. The pancreas furthermore contained only a few islets of Langerhans, which, as in the case of *Unshelm-Kimmelstiel*, had partially undergone pathological change, viz abnormal enlargement. Along with this were also found signs of pancreatitis.

Together with *Vendég*, *Faber* performed some experiments with the glycogen isolated from the liver of this child, in order to control the above mentioned hypothesis and experiments of *Kimmelstiel*. The behavior of this glycogen, however, with regard to its fermentative destruction with diastase preparations, as well as its complete destruction by boiling with diluted HCl, did not differ from that of glycogen preparations which had been prepared in other ways. Thus the

hypothesis of *Kimmelstiel* with regard to the pathological nature of the glycogen in glycogen disease could not be confirmed

Lindsay, Ross and Wigglesworth recently described a case in a French Canadian boy

When seven months old the boy began to vomit, and his abdomen was noticed to be unduly large. He kept on with frequent attacks of vomiting and his abdomen continued to enlarge slowly. At the age of 27 months the child was rather short and gave the impression of being very fat. The nutrition of the arms and legs was, however, poor, muscles were soft and flabby. Mentally he was very placid and coöperative—Systolic murmur at the apex of the heart. Heart not enlarged. Dilated superficial veins over the upper part of the abdomen. Surface of the enormously enlarged liver smooth and firm. Genitalia normal.

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Exchaquet in 1931 described three members of one family—older

boy and twin sisters—with a congenital hypertrophy of the liver and retardation of growth

The author, after investigation of his cases and discussion of the literature, thought it most likely that in his cases the hepatomegalia was caused by an abnormal accumulation of glycogen. The hypoglycemia, the blood sugar curve after ingestion of glucose, the hyperlipemia and hypercholesterolemia, the presence of acetone and diacetic acid in the urine especially one and one half hours after the ingestion of glucose, the acidosis, the normal tolerance for fructose and galactose, all now seem to be in favor of this diagnosis. However, several features encountered in the cases give them a peculiar character. *a*, it is regarded as almost certain by the author that the liver, even at birth, was much enlarged, *b*, though there existed a retardation of growth, the typical impression of an endocrine insufficiency such as is present for the most part in cases of glycogen liver was not present, *c*, all three patients showed a caput Medusae on the abdominal wall and in the twin sisters a little ascites was noticed, *d*, urobilin or urobilinogen was not constantly absent and was even increased in one of the patients, *e*, a symptom now regarded as fairly typical for cirrhotic processes, e.g. an increase of the globulin content of the serum (*Bendien and Snapper*), was very probably present. In every case the author found a much increased protein content of the serum combined with a much increased sedimentation rate. The combination of symptoms present in these cases offers a splendid illustration of the difficulties which the problem of the biochemical recognition of a glycogen liver sometimes presents, especially with regard to the differential diagnosis from cirrhosis of the liver.

Unshelm in 1934 described a doubtful case of glycogen disease, in which X-ray treatment of the liver may have improved the condition.

The child, when seven weeks old, had a distended firm abdomen. At the age of three months the child was badly developed, and showed a network of veins on a very distended abdomen, which was nearly totally filled by a large, smooth, hard tumor (hepatomegalia glycogenica?). The abdomen was treated with Röntgen-rays twice at the same time the child was treated with ultraviolet light. Twelve weeks after the irradiation the liver was still enlarged, but the distention of the abdomen had decreased. At the age of nine months general condition excellent, liver much smaller. Before the irradiation the urine on several occasions contained small quantities of sugar, twice after the ingestion of 10 gm of galactose there was a marked and long-lasting excretion of sugar (!). Two and one half months

after the irradiation there was no more excretion of sugar under similar conditions. Five weeks after the irradiation the blood sugar curve after ingestion of 7.5 gm of glucose was entirely normal. The blood sugar content in the fasting state fluctuated widely, the lowest value found being 53 mgm %. Nine days after the second irradiation subcutaneous injection of 0.5 mgm of adrenalin caused a small elevation of the blood sugar during the second and third hour after the injection (from 53 to 82 mgm %). In repeating this experiment later on, the elevation of the blood sugar became more pronounced, twenty four weeks after the irradiation the blood sugar content rose from 110 mgm % before the injection to 260 mgm % afterwards. In the beginning acetone was always *absent* from the urine, only when the child was nine months old did the urine one to two and one half hours after injection of adrenalin and after a fasting time of nine and one half to eleven hours contain acetone and traces of diacetic acid.

The decrease in size of the congenital liver hypertrophies treated by X rays noted in other cases (*Flppö*) was thus found here, also, and with it went an improvement in the condition of the child. The tendency to acetonuria after the injection of adrenalin, *absent* in the beginning, became manifest later on, when a normal elevation of the blood sugar content had taken place. This result is indeed very peculiar. The author sees some analogy to the case of *Worster-Drought* to be discussed later on — The therapy applied in this doubtful case of glycogen liver will be discussed presently.

Warner reported on a case in a girl, aged five years, perhaps there existed in this case a familial condition.

The girl, when two years old, had a bronchitis, followed by an obstructive jaundice lasting seven days. When the jaundice was clearing up, the abdomen was noted to be extremely large and it remained enlarged. When five years old, the girl weighed only 28 lbs and was only 33½ in in height. The liver was very large, its surface smooth, not tender. Spleen not palpable. When starved, the blood sugar fell to as low as 0.048% and acetone was then found in the urine. Acetone was increased two and one half hours after the ingestion of 20 gm of glucose. During the glucose test no sugar appeared in the urine. The rise of the blood sugar after glucose was about normal. After 4 minims of adrenalin subcutaneously the blood sugar rose very little, as compared with a control child of the same age —

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Van den Bergh's reaction and the fructose test were normal in this case. The child was intelligent with a head relatively large for her small stature, her face was plump which was in contrast to the limbs which were small and flabby — It is peculiar that the occurrence of the condition after jaundice is rarely mentioned in the history of the cases of glycogen liver, as was remarked in the discussion of this case by Dr *Parkes Weber*

Very interesting is the case of *Worster-Drought*, which was demonstrated in 1923 under the title "A case of enlarged liver with persistent acetonuria and diaceturia" It was again described by *Worster-Drought* and *Parkes Weber* in 1933, and once more discussed by *Worster-Drought* in 1935

The patient, a girl, was born in 1910, birth weight, 4900 gm. Between the ages of one and four years there were *epileptiform attacks* occasionally and recurrent attacks of vomiting. A large liver was noticed between the age of two and five years. When ten years old, the child was only 110 cm in height, there was acetone-breath, the liver was very large, the spleen not palpable. No sugar, acetone or diacetic acid were found in the urine, the fructose test was negative. After giving more carbohydrates acetonuria did not appear and the child was irritable and lost appetite. In 1925 the liver gave the impression of having become smaller. In March, 1930, the fasting blood sugar was 0.075%, a delayed fall in the blood sugar curve was noted. There was some infantilism, puberty being retarded until the age of seventeen. In 1932 the child was well developed both physically and mentally. *The liver was no longer enlarged*. In the urine acetone was still present but no diacetic acid or sugar.

In 1935, the patient, now aged twenty-five years, was free from all symptoms. But occasionally there was acetone breath and a trace of acetone in the urine. The liver was not enlarged. Height 5 feet 6½ inches, weight 134 pounds.

One of the other children of the same family died when three years old and from reports *must have had an enlarged liver*. There was, therefore, the possibility of a familial disposition. The case is very possibly one of glycogen liver though the biochemical part of the investigation is rather meagre, the blood sugar was determined for the first time when the patient was twenty years old and no adrenalin test was performed. The hepatomegaly was, however, accompanied by acetonuria. The disappearance of the large liver is highly

interesting This may be an indication of the excellent prognosis in this condition It is also important that with the diminution in size of the liver no glycosuria or diabetes mellitus developed, as in *Parnas* and *Wagner's* case.

Ellis in London has described several cases of extreme hepatomegaly and discussed the possibility of the cases being examples of glycogen disease (see also *Ellis* and *Payne*)

I In one case, a girl, the increase in size of the abdomen was first noted at the age of five weeks At the age of four months an enormously enlarged liver was found, no enlargement of the spleen was noted Liver puncture was unsuccessful in obtaining sufficient tissue for examination No acetone bodies or sugar were found in the urine Blood sugar after four and one half hours fasting was somewhat low, 68 mgm % Blood cholesterol normal Injection of 2½ minims of adrenalin three hours after feeding milk showed only a slight elevation of the blood sugar (maximum rise 28 mgm) In March, 1935, Dr *Ellis* kindly wrote me that at the age of nineteen months the liver in this case had become *very much smaller* The child had progressed normally and appeared to be in excellent health, the typical swollen face of many patients with glycogen disease was lacking In the light of recent publication on biochemical findings in so-called "stéatose hypertrophique" of the liver (we shall refer to this condition more extensively later on), the author was of the opinion that this could represent an example of hypertrophic steatosis with spontaneous remission Acetone bodies have never been found in the urine.—The paternal grandfather of this girl died from diabetes

In the discussion Dr *Helen Mackay* reported an analogous case This was a boy aged five months, whose abdomen had been noticed to be large from the age of one month or perhaps even from birth The liver occupied most of the right side and a large part of the left side of the abdomen Small irregularities could be felt on the surface of the liver, as in Dr *Ellis'* case Van den Bergh test negative, no acetone in the urine, injection of one minim of adrenalin produced a rise of 0.033% in the blood sugar curve Blood glycogen 17 mgm % The child died at home, no autopsy could be done.

II Under the title "Hepatomegalia glycogenica with infantilism in two sisters" Dr *Ellis* in 1934 described sisters, one fourteen, the other nearly twelve years old In the two patients the large size of the abdomen began to excite comment at about two years of age The younger girl was back-

ward in walking and also backward mentally, the elder was nearly normal, mentally and emotionally Both are said to have had a slight *jaundice* once —The elder girl at the age of fourteen years showed about four years' retardation in physical development The greater part of the teeth were still of the first dentition Spleen not palpable No ascites, no jaundice No signs of puberty Blood cholesterol 223 mgm % —The younger girl in 1934 also showed a retardation in physical development of about five years She still had all her first teeth Liver much enlarged Spleen not palpable No jaundice or ascites Blood cholesterol 232 mgm % (in April, 1929, 350 mgm %)

In both patients there was a low fasting blood sugar, traces of acetone in the urine, a low or delayed rise in blood sugar following the injection of adrenalin, a significant rise of blood sugar in the laevulose test, hepatomegaly and infantilism The cases were regarded as examples of glycogen disease In the author's opinion the prolonged slight carbohydrate starvation might have been responsible for the retardation in growth and development

III *Ellis* in 1934 further reported on *three patients* (a brother and two sisters) with hepatomegalia associated with infantilism The boy was eighteen years old At the age of three years he appeared to be well developed The abdomen was greatly distended by the greatly enlarged liver Six months later he had *jaundice* and vomiting of sudden onset, associated with a single severe epistaxis and the appearance of bile in the urine Since early childhood there had been obvious somatic infantilism When eighteen years old the boy appeared well, but had a somewhat muddy complexion, though he was not jaundiced He was then completely infantile as regards genital development and secondary sexual characters Small maxilla, small nose Liver very much enlarged

The girl of fourteen years had, following tonsillitis at eighteen months of age, transient *jaundice* and retardation of growth Mentally normal Abdomen large since birth At the age of fourteen years large, firm and smooth liver Dentition considerably delayed, centers of ossification normal Sella turcica normal Small telangiectases on the face The same muddy complexion as her brother

The girl of eleven years was in every way more nearly normal than the two other patients Her retardation in growth was less marked Dentition delayed Ossification centers and sella turcica normal Liver much enlarged

All three patients showed acetonuria and low fasting blood sugar values. In the two girls an adrenalin test was done, the rise in blood sugar was delayed. Blood cholesterol in the girl of fourteen years 346 mgm %, in the other 208 mgm %.

In the review with *Payne, Ellis* still reported another patient, a girl aged four years, in whom the diagnosis remained doubtful. At the age of two years and eight months an enlarged liver was found and also a slight enlargement of the spleen was noted. The patient showed acetonuria. The adrenalin tests gave different results. The fasting blood sugar was slightly decreased, the blood cholesterol not raised.

Alice King reported a case in a boy aged three years.

The size of the abdomen impeded walking. Apart from occasional attacks of bronchitis the child was healthy. The abdominal enlargement was the only abnormality and was caused by an enormous enlargement of the liver. The surface was smooth. Spleen was not palpable. Urine contained occasionally traces of acetone, never sugar. Blood glycogen 17.6 mgm %. No jaundice. Lowest fasting blood sugar 0.079%. After 30 gm of glucose maximal rise to 0.152%. After 3 minims of adrenalin a rise of 0.061%, and only a trace of acetone in urine. After 30 gm of laevulose normal blood sugar curve.

Naish and Gumpert reported a case in a boy of five years.

The following symptoms were present: hepatomegaly, hypoglycemia in fasting condition, ketonuria, abnormal glucose tolerance curve, no elevation of blood sugar after injection of adrenalin. The feces in this case contained large amounts of starch, but there was no absence of active amylase. The question is raised as to how far conversion of glycogen into glucose in the liver, and the digestion of starch in the intestine are impaired in this condition.

From Australia several typical cases have been reported. *Solomon and Anderson* in 1933 reported a case.

The patient was first seen in July 1932, at the age of 22 months. The parents were wondering why the legs of the child were so slim.

The diagnosis of glycogen disease was founded on the presence of a uniform and non-painful enlargement of the liver, absence of enlarged spleen and jaundice, presence of ketonuria, later on combined with hypoglycemia. The fasting blood sugar was 0.1%, two hours after breakfast it

was 0.124% Blood cholesterol 126 mgm % Severe *lipemia* Slight anemia, moderate leucocytosis The *lipemia* disappeared on a fat-poor diet In February, 1933, the mother stated that the child had commenced taking "turns" The episodes resembled mild epileptiform seizures They always occurred between five and six o'clock in the morning The urine then contained *acetone* and the child gave fasting blood sugar values of 0.056% with a rise to 0.088% two hours after 120 cc of sweetened milk had been given The seizures disappeared on feeding the child with an abundance of glucose at night.

The epileptiform seizures combined with hypoglycemia and ketonuria which were present in this case are of interest Also in *Worster-Drought's* patients fits were present between the age of one and four years They were compared to the hypoglycemic attacks caused by an overdosage of insulin The fact that these attacks in their case were relieved by the administration of glucose, which must also pass the liver, led the authors to the question "Is there some chemical difference between the glucose given medicinally and the glucose formed from the breaking down of glycogen?" The authors kindly wrote to us about the further course In February, 1935, the child was quite well Liver smaller in comparison with that of a child who is growing normally "Yesterday had first hypoglycemic attacks after twelve months Very slight, no convulsion, obviously due to a lot of playing round on a very hot day and using up the sugar reserve" In a publication of March, 1935, *Anderson* wrote that the ketonuria was less, the size of the liver had decreased and the tenseness within its capsule had definitely diminished

In June, 1934, *Anderson* and *Vickery* described a case in a girl of four years

The mother stated that the child had been developing a huge abdomen since the age of eighteen months She grew tired when taken for a walk and had a waddling gait She was well nourished and fat-faced, but the limbs were comparatively thinner than the rest of the body and the limb muscles lacked normal tone Length and weight about corresponded to age The veins of the abdominal wall were very prominent The liver margin could be felt 3.75 cm below the umbilicus Acetone reaction in urine strongly positive, the child's breath smelled of acetone Fasting blood sugar 0.072%, after 12 gm of glucose it rose only to 0.086% No rise

of blood sugar after injection of adrenalin. No lipemia and no hypoglycemic convulsions. Blood sugar during the day never above 0.132%. During a period of voluntary starvation slight glycosuria was noticed, without a high blood sugar content.

With a relatively high fat diet this glycosuria was not abolished, so that the sugar was not being used in the combustion of fat. During this period the ketone bodies were at a lower level than when the child was on a mixed diet.

The authors put the question whether there is a central mechanism controlling carbohydrate storage in the *diencephalon*. "There are symptoms," they say, "suggesting this in various *pituitary disorders*, and the fact that in all proven cases so far the patients have been girls of similar habitus and appearance, may suggest this common basis"—Anderson, in March, 1935, stated that the girl had recently suffered from an attack of *catarrhal jaundice*. She had fever and vomited several times. During this illness her ketonuria grew less, the blood sugar values remained at the same level and the size of the liver diminished. After the illness the ketonuria was as pronounced as before. It seemed thus that during the fever the utilization of glucose was markedly accelerated.

Holmes & Court and Bray in 1934 gave a description of a case in a child, 3½ years old.

The patient, a girl, had been ill from the age of three months. She had had a *fit* at that time. At the age of six months the abdomen had been markedly enlarged. In November, 1931, *the abdomen had been opened* and a general enlargement of the liver had been reported. The liver was normal in color and consistency. In May, 1933, the fits and vomiting, previously present, had diminished. The *mental development* was then *retarded*. Liver grossly enlarged. Skeletal musculature flaccid and toneless. Acetonuria constantly present. No glycosuria. Fasting blood sugar 0.057%. After giving fructose it had risen in two hours to 0.093%, after three hours acetonuria was still strongly positive. After adrenalin no rise of the blood sugar occurred in thirty minutes.

Biedermann and Hertz have reported two cases of glycogen liver disease and, especially, Hertz has made a number of valuable investigations on the metabolism.

The patient of Hertz was an only child, a boy, with a birth weight of about 4 kilos. The increase of the abdominal circumference was noticed by the parents in the second quarter year of life. Marked reduction in the amount of food had no influence on the abdominal circumference. The child often had epistaxis and headaches without vomiting. Intelligence normal.—At the age of six years, the diagnosis of enlarged liver and spleen was made for the first time, the very much enlarged left lobe of the liver being mistaken for the spleen. Walking became more and more difficult. Severe *genu valgum* developed. Hands and feet plump and short.—The circumference of the head at the age of twelve years was much *too small* for the age, in relation to length the circumference was, however, too large, the child being much too small.—Three times the boy had a fracture of the femur, caused by slight trauma, which healed normally within a reasonable time.—At the age of eight years the skin of the face had become puffed up, on the cheeks were telangiectases. Never icteric or subicteric. Pale color. Musculature very hypotonic. Thyroid gland small. Testes atrophic. *Mons pubis rich in fat*, in contrast to the lack of fat elsewhere.—In the morning urine acetone often present, never sugar. Hypochromic anemia. Leukopenia with relative lymphocytosis. Retardation of the development of the skeleton. *Severe osteoporosis*. Transverse lines near the epiphyses. Sella turcica normal.

The patient of *Biedermann* was also an only child. At the age of eight months he had epileptic convulsions, which were reported two to three times up to his third year. Twice jaundiced. Infraction of the right arm, distortion of the right leg. Intelligence normal. Often epistaxis. When eleven and one half years old, the patient was 12 cm. too small and for his length 3 kilos too heavy. Rather marked adiposity, especially in the neighborhood of the shoulders and the upper arms and hips. Musculature soft. Vessels distinct upon thorax and abdomen. Kyphosis. *Extremities slender*. Circumference of the head somewhat too small. Marked adiposity of the abdomen. Liver palpable four fingers below the costal margin. Spleen not felt. Genital organs somewhat too small. Acetone present in urine on a day of vegetable diet, after adrenalin and after bilirubin injection. After hyperventilation no epileptic convulsions. The attacks recurred spontaneously.

In the first case the patient, therefore, closely resembled a dwarf with eunuchoid accumulation of fat at the mons pubis and severe osteoporosis which gave rise to fractures. In the second case the re-

tardation of growth was less marked and there existed an adiposity of the trunk.

Both patients showed a normal reaction as regards pulse and blood pressure to the injection of adrenalin. The blood sugar after injection of 0.5 mgm adrenalin while fasting remained unchanged, after 1 mgm. there was a slow and not marked rise of blood sugar. If the injection was carried out four and one half hours after a meal, no effect at all was observed (persistence of influence of insulin secretion provoked by food?)

An investigation to determine the presence of a so-called initial *insulin hyperglycemia*, which might be of value for judging the presence of a glycogen depot in the liver (*Birger*) was carried out in one patient. The rise of blood sugar was within the lower range of normal.

The blood glycogen of the fasting blood in the patient of *Hertz* was repeatedly found to be increased. In the urine of this patient acetone was not regularly present while the patient was fasting. After giving glucose or fructose marked acetonuria persisted for at least one hour. The patient was found to be sensitive to small amounts of insulin. In a combined sugar-water insulin test according to the method of *Althausen-Munck* this sensitivity to insulin was not noted. The result of this test which was performed in both patients, is evidence, in the author's opinion, against a beginning cirrhosis of the liver.

Hertz' patient had a low fasting blood sugar value (46-47 mgm %) but never any hypoglycemic symptoms. In *Biedermann's* case the values varied 53-83 mgm.%. Both patients showed much increased tolerance to sugar but never any glycosuria. The blood sugar curves showed pathologic hyperglycemic values, prolonged return to original values, biphasic curve (*Biedermann's* case). In *Hertz*' case the blood sugar curve after fructose was normal, it was abnormal in *Biedermann's* case.

In one patient (*Hertz*' case) the *esterification with phosphoric acid* after giving glucose and fructose was studied from the phosphate excretion. This excretion was much increased, as in diabetes.

As regards the *nitrogen metabolism* this was found in *Hertz*' case to be normal, notwithstanding a highly increased basal metabolism! The amino-acid metabolism was normal in both patients, a fact which, also, spoke against a *liver cirrhosis*. The creatin-creatinine relation in the urine was abnormally high in *Hertl.*' case. The explanation of this fact is still not clear.

Investigation of blood serum and urine demonstrated only a small acidotic deviation of the metabolism which was of a temporary nature. The

water metabolism was probably normal in both cases. The blood diastase content was normal. In the urine large amounts of diastase were present. Glycolysis of the blood was normal.

The *lipase* content of the serum was distinctly increased in *Hertz*' case, principally caused by an increased quinine resistant lipase. However, the author is *a priori* not inclined to explain this finding, as is usually done, on the basis of severe liver-cell damage.

Von Gierke and *van Creveld* on different grounds had stated the hypothesis that in glycogen disease one has to do with the continuation of a fetal condition in the liver. This suggestion gave *Hertz* the impetus to study the postmortem disappearance of glycogen in the liver of new-born child and fetus, especially as regards velocity and degree of glycogenolysis under different external circumstances. The liver was investigated in a way analogous to that used by *Schonheimer* and *Unshelm* in cases of glycogen liver and afterwards by *van Creveld* in a case of glycogen heart. The influence of the pH of the medium was very distinct. As early as the second quarter of pregnancy glycogenolysis could be demonstrated in the fetal liver. This occurred, however, distinctly more slowly than in older fetuses and in new-born children. A direct comparison with the findings of *Schonheimer* in his autolysis experiment could not be made. It seemed probable that this post-mortem glycogenolysis found in glycogen liver was smaller than that in a fetus of six months.

Recently *Hertz* has again studied this glycogenolysis in liver tissue in a case of glycogen heart described with *Jeckeln* (see chapter 3). It appeared that the disappearance of glycogen from the liver tissue, kept under optimal conditions for diastatic activity (phosphate buffer of pH 6.9-6.5, temperature 37°C) was greater after the addition of a pure diastase preparation which was free from proteolytic enzymes. In the author's opinion it is, therefore, improbable that this increased glycogenolysis is due to a splitting of glycogen which should be attached in an abnormal way to protein, as *Unshelm* proposed. On different grounds *Hertz* has accepted the view that in his case of glycogen liver there existed a decreased activity of the neuro-hypophysis. Against a hypophyseal disturbance was the abnormal high basal metabolism, the absence of visible changes in the sella turcica and other hypophyseal symptoms, and the peculiar proportion of the extremities.

in relation to the trunk. However, in his case of glycogen heart the basal metabolism without doubt was strongly decreased, whereas the liver also in this case contained much glycogen

As regards the possibility of a growth disturbance of the cerebrum, *Hertz* is of the opinion that in his case there were present some symptoms which might suggest that the brain was not functioning quite normally (small circumference of the skull) An encephalogram could not be made, in *Biedermann's* case the intelligence was normal

The growth disturbance occurring in glycogen disease can be either the type of a "dystrophia" caused by an internal carbohydrate-hunger, or present the characteristics of a disturbed internal secretion, or there can be a mixed picture In infants and young children the influence of the dystrophia would predominate and give rise to retardation of growth in length, and to slender extremities—The fact that in glycogen disease we have to do with a general disease metabolism and not with an isolated liver disease, in *Hertz's* opinion, makes necessary a separation of the growth disturbance in this disease from the so-called hepatic infantilism (*Lereboullet, Pfaundler*) etc (see below)

Unshelm, however, starting from the idea that in glycogen disease important functions of the liver are greatly disturbed, does not make the same separation of the growth disturbances The growth disturbances occurring in cases of glycogen disease may show marked differences, as in all cases of liver diseases The author separates a type, occurring in children in which the liver disease started at a very early age, from a type occurring in children who fell ill at a later age The irregularity in the normal velocity of the processes of development occurring in the two types causes the patients to give a very varying picture as regards their development To the signs of the hepatic disturbance of growth belong, therefore, the retardation of the growth in stature, the persistence of proportions of an earlier state of development and the rudimentary and varying growth of different parts of the body However, all organs and tissues which are influenced by growth may show consequences of the growth disturbances

From this point of view a discussion is given of the changes observed in cases of glycogen disease in the development of the fat depot, musculature, condition of the skin, primary and secondary sexual

characteristics, osseous system, teeth, gait and muscular and mental functions. The fundamental cause of the disturbances of growth observed in diseases of the liver is still unknown. It is generally believed to have nothing to do with a primary disease of one or more glands of internal secretion.

Rauh and *Zelson* in 1934 described a case in an Italian boy.

At the age of eight months the abdomen seemed to be larger than normal. Up to the age of twenty months, when the boy came into the clinic, the abdomen had increased in size. No other complaints. The edge of the liver was felt at about 5 cm. below the umbilicus in the right mammary line. The left lobe of the liver extended about 7 cm. below the costal margin in the left mammary line. Liver of normal form, not tender, edge sharp, surface smooth. Spleen not palpable. The boy was underdeveloped.

Urine. Acetone on repeated examinations, amount of diastatic ferment greatly increased. No glycosuria. Blood amylase lowered. No free glycogen in the blood. Fasting blood sugar 40–65 mgm per 100 cc. Blood sugar curve in two tests biphasic, prolonged curve with maximal rise to 100 or 110 mgm after two hours—After adrenalin the blood sugar rose in one test from 45 to 115 mgm % in one hour, in the second test from 65 to 120 mgm % in one and one half hours. After 2 units of insulin almost no reduction of blood sugar, after 5 units the blood sugar rose from 60 mgm in fifteen minutes to 70 mgm % followed by a long-lasting reduction—Total cholesterol increased. Ratio of total cholesterol to cholesterol-ester normal. Galactose and bromosulphonphthalein test normal. Serologic tests negative. Transverse lines in the metaphyses of long bones.

No increase of the blood sugar or change in the size of the liver was observed after a diet high in carbohydrates, or after the administration of epinephrine or thyroid. In three months the child grew 3 cm. in height, the circumference of the abdomen increased 4 cm. Never any spontaneous hypoglycemic reactions. Breath frequently had the odor of acetone. The child preferred food rich in carbohydrates, especially potatoes.

Based on *Lesser's* theory, *Rauh* and *Zelson* think it conceivable that the excessive deposit of glycogen within the liver cells may interfere with the normal glycolytic function of these cells by disturbing their colloidal state. An increased permeability of the kidney cells to amylase in glycogen disease is accepted as a possible explanation of the increased excretion of amylase.

Wilder described a case in a girl of three and one half years.

At nine months and at eighteen months the patient had an acute upper respiratory infection with fever and convulsions Whooping cough at two years, measles at two years and a half At about the age of six months the mother thought that the baby was fatter than she ought to be and noticed that head and abdomen were disproportionately larger than the extremities As she grew older, the child tired more rapidly than her companions At three and a half years cheerful, alert, with quick response to attention Round head with fat face, very short neck and prominent brow Abdomen protruded markedly Trunk fat with much fat at the base of the neck posteriorly Legs and arms relatively thin and somewhat short. Genu valgum Twenty normal teeth Moderate amount of fine lanugo hair Abdomen 62 cm in circumference at the umbilicus Liver markedly enlarged, smooth, somewhat soft, not tender Spleen not palpable Acetonuria was constant daily, though variable in single specimens—Blood lipoids normal, cholesterol not increased Fasting blood sugar, glucose tolerance test, epinephrin, insulin and pituitrin tests normal The liver water storage ability appeared greatly impaired X ray investigation of the abdomen showed a very large liver with evident enlargement of the *right kidney*

X-ray examination showed that the *sella turcica* was within normal limits but depressed, along with the whole middle cranial fossa The petrous portion of the temporal bone was also depressed This was taken by *Wilder* to indicate the presence of an internal hydrocephalus, probably more marked in the third ventricle He raised the question whether this type of hepatomegaly might result from internal hydrocephalus with pressure changes in the region of hypothalamus and pituitary gland—It seemed to *Wilder* that the diagnosis of hepatomegaly glycogenica was most probable in this case.

Erben and *Kiister* in 1936 described a case in a boy of three and three quarters years

He showed all the clinical symptoms which have been found in the majority of the cases of glycogen liver (hypoglycemia in fasting condition, ketonuria, absence of rise of blood sugar after injection of adrenalin, etc.) The boy gave the impression of a patient suffering from adiposogenital dystrophy In the X-ray the *sella turcica* showed distinct abnormalities it was very flat and enlarged. Neurological or ophthalmological symptoms were absent, however, perhaps in an earlier stage of the disease symptoms of an intracranial process were present.

Krakower in 1936 described two cases of glycogen liver with autopsy findings and reported the result of a biopsy of the liver in a third case

The first case was that of a boy, aged five months, who since birth had had a large abdomen, which had progressively increased in size. The boy died on the third day after admission into the hospital. Blood withdrawn on the third day was creamy and opaque, grayish yellow in color. The serum cholesterol was 394 mgm %, the carbondioxide combining power 24 volumes %. Acetonuria was present. At the autopsy the liver was greatly enlarged (weight 705 gm, normal 188 gm). Both kidneys were large (the right kidney weighed 46 gm, the left one 48 gm, normal weight 25 gm). On microscopic examination of the heart only occasional fibers contained glycogen. The pancreas islets were abundant and large. The liver cells were large of a plantlike type. The cells were infiltrated with glycogen and fat. The cells of the convoluted tubules of the kidney were of the plantlike type and were massively infiltrated with glycogen. After several months of fixation in Pick's solution the liver and kidneys in this case still contained 3.04% and 11.5% respectively of glycogen in terms of dry weight. These values exceed by far those of the normal range. The fat content by dry weight of the liver was still more striking, amounting to 52.3%. Spleen and bone marrow probably contained stored lipoids in large pale cells.

The second case was that of a Jewish boy of one year, who also died on the third day after admission into the hospital. At the autopsy the liver appeared greatly enlarged and both kidneys were greatly increased in size. The liver weighed 1213 gm (normal 288), the right kidney 77 gm (normal 36), the left one 67 gm (normal 35). At the microscopical examination there was found among other things glycogenic infiltration of liver and kidney, marked fatty infiltration of the liver and probably lipid containing cells in spleen and bone marrow.

The third case was that of a girl of eight years, who had an enlarged abdomen since the age of six months. A sister of the patient had died when four years old from apparently a similar condition. The girl showed retardation of growth. The extremities were delicate and slender, the cheeks were full, but the subcutaneous fat was meager elsewhere. The liver always was greatly enlarged. Occasional epistaxis. Three weeks before admission the patient developed extreme dyspnea and anorexia. Acetonuria and hypoglycemia were present, there was no response to adrenalin. The patient died within a month after the admission to the hospital. Only the biopsy of the liver, skin and muscle could be performed. The liver contained a large amount of glycogen and also fat.

In all three cases there was thus a marked degree of fatty infiltration of the liver in addition to the glycogen infiltration. The author is of the opinion that the large pale cells in spleen and bone marrow, also, stored lipoids, though this could not be demonstrated—An analogy is drawn by the author between the clinical findings (lipemia, ketosis) and the pathological findings (among others fatty infiltration of the liver, fat-laden large cells in the spleen), pointing to a disturbed fat metabolism in glycogen disease corresponding to that found in diabetes mellitus.

Harnapp in 1936 reported on two cases of glycogen liver.

In the first case, a boy, the enlargement of the liver had been progressive since the age of seven months. At the age of two years and five months the boy showed an enormously enlarged liver. Pirquet test strongly positive. The metabolism showed the well-known features with the exception of a fairly large elevation of the blood sugar after injection of adrenalin and on one occasion an abnormal elevation of the blood sugar after 30 gm. of fructose. The excretion of phosphates in the urine (*van Creveld* and *Hertz*) after 30 gm. of glucose showed a constant decrease, after giving 50 gm. of glucose, the excretion of phosphates the first time was slightly increased, the second time it remained unchanged. After giving fructose or galactose the excretion of phosphates slightly increased. The basal metabolism determined by *von Grafe's* method, was slightly increased ($\pm 9\%$). Blood cholesterol 408 mgm.%, esters 274 mgm.%. Serum diastase normal. Diastase in urine slightly increased. The boy showed sensitiveness to infections, which were always accompanied by a severe ketonuria. Röntgen irradiation of the liver (*Unshelm*) was followed by a decrease in volume of the liver during four or five days after the irradiation. However, in two to three weeks the liver regained its original size. The general condition of the boy and his carbohydrate metabolism were not influenced by this irradiation.

The second case was that of a boy whose grandfather was suffering from diabetes mellitus. At the age of four months the presence of a very much enlarged liver was already established. Hypoglycemia, acetonuria and urobilinuria were absent. Tolerance tests with different sugars gave normal results. The adrenalin effect on the blood sugar content (by the author regarded as being normal) was small. Fat tolerance test (*Bürger* and *Habs*), which should be of differential diagnostic value between glycogen liver and liver cirrhosis (*Beumer* and *Loeschke*), gave normal results. A biopsy of the liver was performed. The histological examination of the

preparation (*Hamperl*) showed excessive accumulation of glycogen in the liver cells and correspondence in other particulars, also, with the findings in definite cases of glycogen liver. The border of the excised piece of liver showed, however, cell infiltrations which made an exact anatomic diagnosis impossible.

Harnapp is convinced that he had to deal in this infant with a case of glycogen disease. The size of the liver decreased distinctly after this biopsy and still more after a further roentgen irradiation. The author cites this case as an example that glycogen liver may be present whereas the well-known peculiarities in the metabolism are all absent.

Sundal described a case in a girl of twelve years, whose father was a diabetic. The enlargement of the liver was present since birth. At the age of about two years there was a brief attack of jaundice. The retardation of growth appeared early in childhood. The patient showed hypophosphatemia and further nearly all deviations from the normal in the metabolism that we found in the first clinically described case in 1928. The glycogen content of the blood was 17.6 mgm per cent.

Very recently *von Gierke* reported the results of the autopsy of a case of hepatomegalia glycogenica in a girl of nearly fifteen years, who died from an otogenic meningitis.

During life the girl was said to have shown arrest of growth, retardation of mental development, sensitiveness to infections, anorexia (but preference for bread) and often abdominal complaints. Apparently nothing in particular was known with regard to the metabolism. At the autopsy was found hepatomegalia glycogenica (weight of the liver 2750 gm, e.g. about two and one-half times the normal weight) and infantilism. The amount of connective tissue in the liver was not increased. The liver showed small islets of normal liver tissue where glycogen was absent or nearly absent. The significance of these islets is uncertain. The possibility exists that they represent efforts at spontaneous recovery. Heart and kidneys were not enlarged and only the kidneys showed a slight glycogenic infiltration. Histologically, the heart muscle fibers were normal, as also the striated muscle fibers. Pancreas, thyroid and hypophysis were normal. The adrenals contained only a slight amount of lipid. The presence of glycogen in the adrenals, however, was very remarkable, though in the author's opinion this need not have etiologic significance.

This case reports the oldest individual with glycogen liver who came to autopsy (The first patient with glycogen liver clinically described by us in 1928, is still well at sixteen years of age.)

b (Congenital) hypertrophic steatosis of the liver

In a former discussion of the rôle of glycogen as a cause of the enlargement of an organ (1932) we pointed to the fact that before one is justified in making the diagnosis of glycogen liver, it is necessary to differentiate the condition from different affections of the liver and from other system diseases. We mentioned, especially, cirrhosis of the liver and a definite form of chronic, very pronounced hypertrophy of the liver limited to that organ, caused by a large accumulation of fat.

Though we shall devote a special section to the differential diagnosis of glycogen disease, we prefer to discuss the recently published cases of congenital hypertrophic steatosis of the liver at this point, in connection with the cases of glycogen liver just reviewed. This hypertrophy of the liver in children, caused by excessive accumulation of fat, has been described as a solitary and as a familial affection by Björum. In 1927 he described four children of a family of eleven. All four children died of intercurrent infection within the first two years of life. At autopsy an enormous fatty liver was found in all cases. Intoxication was excluded. A blood sugar determination was carried out in only one of the children, it gave an average fasting value of 80 mgm per 100 cc.

Four years later Debré and Sémelaigne under the title "Stéatose hépatique massive du nourrisson" described a child with hypertrophy of the liver which at biopsy proved to be largely due to an extensive fatty degeneration of the liver cells. The blood sugar content at that time was not determined. In 1932 Grenet, Levent and Mourrut described an analogous case (see later on). It is to the credit of Debré and his co-workers (Nachmansohn and Gilbrin, later on, Sémelaigne) that, after the first clinical descriptions of patients with glycogen disease had appeared, they made an extensive comparative examination of their patient, described in 1930, having a hypertrophy of the liver caused by the accumulation of fat, and of three other patients showing hypertrophy of the liver, very probably caused by accumu-

lation of glycogen It should be noted that according to the French investigator a distinct separation of both diseases is not to be made *Debré* introduced the idea "*hépatomégalie polycorrique*" (from *πολύς*, much and *κόσος*, saturation), in order to designate a hypertrophy of the liver, caused by a combined pathologic accumulation of two different reserve substances (glycogen and fat) Either there should exist only an accumulation of glycogen in the liver or there should be, in addition to this, an accumulation of fats or an accumulation of fats alone should be present In all these cases the clinical pictures should show a very great resemblance, so that differentiation would be difficult and the deviations in the metabolism from the normal ought not to differ essentially The various cases showing these divergent conditions should, according to *Debré*, be grouped under one name, and he introduced for that purpose the term, "polycorrique" Nosologically, hypertrophic steatosis and glycogen liver would thus belong together *Debré* not only applied the term "polycorrique" to the cases of liver hypertrophy as the result of accumulation of glycogen, fats or both together, but also to hypertrophy of other organs from accumulation of these reserve substances

Debré's conception has found favor with *Frössinger* *Comby*, however, has stressed the separation of hypertrophic steatosis and glycogen liver According to *Debré* and co-workers these "hypertrophies polycorriques" should be sharply separated from the congenital hypertrophic cirrhoses and from the reticulo-endothelioses in as far as they manifest themselves with a marked liver hypertrophy (disease of *Gaucher*, of *Niemann-Pick* and the xanthomatoses with liver enlargement)

In the case just mentioned and described in 1930 by *Debré* and *Sémelaigne* the authors had to do with a child who had suffered from attacks of fever at the age of ten months and, when five years old, had an enormous hypertrophy of the liver without splenomegaly, mental and bodily development were in other respects normal The possibility that the fatty infiltration in the liver cells was caused in this case by an infection was rejected This case, in which the existence of fatty liver was established by biopsy, differed, however, from the other three cases described by *Debré* and co-workers in which no biopsy was made, in that the hepatomegaly had not developed steadily

and insidiously without fever, abdominal pain and other disturbances, as it does in most cases of glycogen liver. Apart from this difference the four children showed a great resemblance in external symptoms to patients with glycogen liver. All four had the typical marked enlargement of the liver with smooth surface and a homogeneous firm consistency and without tenderness to touch. In all four the spleen could not be felt. In all four a disturbance in growth was present but it varied in degree, the child whose hepatomegaly was proved to be on a fat basis was the one in whom the retardation in growth was the least.

Debré and his co-workers examined the metabolism of carbohydrates and lipoids in their patients. Three of the four patients showed a marked hyperlipemia and two of these three a pronounced hypercholesterinemia. In the child in whom biopsy of the liver had been performed the lipid and cholesterol content of the blood were about normal. This child, as well as two of the others, had doubly refractile lipid substances in the urine. As regards the disturbances in the carbohydrate metabolism found in his cases of "hépatomégalie polycornue," *Debré* concluded that one could distinguish two types (a) cases showing analogous disturbances such as are found in suprarenal insufficiency, (b) cases showing disturbances resembling more or less a pre-diabetic condition.

The patient in whom a biopsy of the liver had been performed probably belonged to the type under a. The fasting blood sugar content in this case was 0.06%. Following glucose ingestion the blood sugar showed almost no elevation. After the injection of adrenalin the blood sugar rose slightly. The presence of acetonuria in this patient is uncertain.

The question of the possibility of separation of cases of hypertrophy of the liver due to massive fatty infiltration from cases of glycogen liver, recently has been studied also by other authors.

Clinically *Debré's* cases showed the following peculiarities. The first child showed disturbances in the mental development, could not walk in the normal way and suffered from tonic-clonic convulsions. The fourth patient also had a very peculiar way of walking, reminding one of the gait in certain of the myopathies. The neurologic examination in the first and third cases revealed no abnormalities. At times the patients showed a

disturbance of the functions of liver and kidney. Thus the third and fourth patients manifested a transient jaundice with bile substances in the urine, the first child almost constantly passed rather large quantities of bile salts in the urine. In the first three patients a marked urobilinuria existed most of the time. The fourth patient had a transient purpura. All patients showed repeatedly slight albuminuria, the fourth patient, moreover, a cylindruria. —Furthermore, the *second and third patients*, who clinically bore such a great resemblance, *were brother and sister*. —No one of the four children exhibited symptoms of obstruction of the portal vein (caput Medusae, ascites, splenomegaly), the concentration of the proteins of the serum was not changed. Tests for lues and tuberculosis were negative.

In the case of *Grenet, Levent and Mourrut*, described in 1932, the authors had to do with a boy of nine and a half years in whom the enormous enlargement of the liver seems to have developed about the age of eighteen months. In June, 1926, an exploratory laparotomy with biopsy of the liver was performed.

The father of the child suffered from diabetes, one sister from epileptic attacks. The child himself showed symptoms of congenital syphilis. When four months old he suffered from convulsions and diarrhoea, shortly before the exploratory laparotomy in 1926 there was diarrhoea with fever and epistaxis. At operation the liver proved to be of firm consistency with localized hard spots. Histologically, the greatly enlarged liver cells proved to be overfilled with fat, glycogen was not found. The child showed retardation of growth and an inclination to adiposity. In 1932 he suffered from epistaxis and then for the first time glycosuria was established (10.5 gm per liter). For several days previously no sugar had been found in the urine but traces of acetone were encountered. Blood sugar content (in fasting state?) 0.86%. One hour after the ingestion of 100 gm of glucose the urine contained 25 gm of sugar per liter. *Grenet* himself rejects the possibility that this could be a case of "stéatose hépatique massive."

Though this clinical picture shows some resemblance to that in glycogen disease, we nevertheless are of the opinion that there are differences on important points. We mention here the hereditary lues, the fever, the repeated marked epistaxis and the marked glycosuria occurring in a later stage, the heterogeneous consistency of the liver and certain abnormalities found histologically in the blood vessels and bile capillaries and in the liver itself. Extensive study of the

metabolism, which should lead to a better comparison, was not carried out in this case

Such a study of the metabolism has indeed been carried out in the case of liver hypertrophy due to extensive fatty infiltration, described in 1934 by *Kramer, Grayzel and Solomon*

This was a female infant, aged six months, who was brought to the clinic because she gained in weight slowly and had a large abdomen. For three days after birth she had shown slight cyanosis and had suffered from a generalized convulsion twice, when one and three months old. In the following three months she had five or six attacks described as short fainting spells. When six months old the child could not sit without support or hold her head up steadily. The head was not large in proportion to the chest. The liver edge was felt three inches below the costal margin. Slight irregular fever. Examination of the blood revealed a very low fasting blood sugar value (on one occasion 18 mgm per cent), with a comparatively marked elevation after the intake of glucose, and a prolonged curve (no hyperglycemia). Injection of adrenalin had no effect on the blood sugar value. Sugar or ketone bodies were never present in the urine. No gross lipemia or increase of cholesterol in the blood. Blood sugar after levulose showed no abnormal rise.—The child died at the age of eight months after having shown symptoms of bronchopneumonia with severe convulsions.

At the autopsy a diffusely enlarged fatty liver (630 gm) was found. Microscopically there was extensive fat replacement throughout the entire sections of the liver. Normal liver cells were nowhere to be found. *No evidence of glycogen in liver or heart.* Kidneys, spleen, pancreas and adrenals normal. An inability to form glycogen from glucose, an aglycogenesis, is accepted as the fundamental defect. The inability to transform in a normal way the glucose in the portal circulation might have resulted in its conversion into fat. The hepatic function, as far as other metabolic processes were concerned, was apparently normal.

Undoubtedly there are present in this case some points which until recently were accepted as being more or less typical for the metabolism in glycogen disease: namely the combination of hypoglycemia and the lack of an elevation of the blood sugar content after injection of adrenalin. Furthermore, the constant absence of acetone in the urine deserves special attention (see under ketosis). Moreover, the enlargement of the liver in this child did not develop, as it does usually in glycogen disease, gradually and unobserved without any interfer-

ence with health. In the anamnesis we find mentioned many facts usually absent in children with glycogen disease: very poor feeding, poor growth, poor appetite, repeated general convulsions. Fever cannot be excluded, during the whole time of nursing there was fever of varying degree together with leucocytosis and slight anemia. These factors might explain the development of a fatty liver.

c. Animal experiments

As the result of the publications of a clinical and pathological nature dealing with glycogen disease, *Junkersdorf* drew attention to his own former researches and those of his co-workers, and to older experiments, among others those of *Schonendorff*. *Junkersdorf* and his collaborators found in animal (dog) experiments that by means of a diet (so constructed that the protein content in itself was sufficient to supply the caloric requirement, and containing, moreover, a large quantity of carbohydrates), the glycogen content of the liver could be increased to an important extent, and that this increase was accompanied by a marked enlargement of the liver. The younger the animal, the earlier occurred the increase in weight of the liver, and also the higher the glycogen content (highest content 21.52%, in an adult dog 15.21%). In the stage when the liver was overfilled with glycogen there existed, three hours after the feeding, a marked hypoglycemia, which under normal conditions was never found in those animals. The symptoms of hyperinsulinism were lacking, although the investigators attached great importance to insulin in explanation of the occurrence of this condition. In older as well as in younger animals there was found, furthermore, a distinct elevation of the *glycogen content of the blood*, which however also occurred earlier and to a more marked degree in younger animals (*Bong*).

In this early occurrence in young animals of glycogen accumulation with its accompanying enlargement of the liver, *Junkersdorf* sees an analogy with glycogen disease in man, which also occurs early in life, that is, in the period of growth. This should speak in favor of the conception that in this early period of life there exists a predisposition to the accumulation of glycogen.

Junkersdorf weighs the possibility that perhaps a preceding, unobserved fault in the diet may play a rôle in the onset of glycogen

disease. Pediatricians know of cases in which an excessive appetite was the cause of a temporary hepatomegaly. In this connection we may, also, mention the very pronounced enlargement of the liver established in the rare case of chronic galactemia, described by *Mason* and *Turner*. Here the size of the liver decreased as soon as the galactose, which could not be sufficiently destroyed by the patient, was no longer offered in excess (in the form of lactose in the milk) — In the cases of glycogen liver a relation between the enlargement of the liver and a too rich diet has often been considered, but the histories of the cases have not revealed any constant finding of that sort and, moreover, restriction of the food supply did *not* cause a decrease in the size of the liver.

Finally, *Junkersdorf* points to the fact that in the animal experiments it is possible first to increase the glycogen content of the liver (and muscles) by fattening the animals, and that this increase will disappear subsequent to the employment of a one-sided protein diet, at the same time the lowered blood sugar content will increase.

However important these investigations are in themselves, they are not of significant importance for the problem of glycogen disease, firstly, because in our cases and those of others there were no peculiarities in the preceding diets of the patients, secondly, because there exists for the most part a great difference between the consistency of the liver which is enlarged owing to the accumulation of glycogen as a consequence of the fattening, and the consistency of that organ in glycogen disease. Further, it is highly improbable that glycogen accumulated in the fatty liver should possess after death analogous properties to the glycogen in glycogen disease. If so, it would mean that such glycogen should be very fixed and difficult to mobilize. Nevertheless, these experiments of *Junkersdorf* deserve our attention.

Of interest in connection with the possible relation between glycogen and fatty liver is the experience that when the excessive supply of carbohydrates in the experiments of *Junkersdorf* and co-workers was continued over a long period, then the glycogen content of the liver decreased again, whereas the content of fat increased.

Junkersdorf explained the hypoglycemia as due to a disturbance in the blood sugar regulating function of the liver cells as a result of their being overcharged with reserve glycogen, a mechanical explanation!

The overcharge should be primary, for also in excessive overcharge with fat in the liver cells as a result of excessive fat supply an analogous hypoglycemia was found, a condition which disappeared when the fat supply was greatly restricted (compare the hypoglycemia found respectively in glycogen liver and in fatty liver in children)

The *changes found in the glycogen content of the blood* in these animal experiments also deserve attention. In glycogen disease we have to deal with such changes, since *Schonheimer* could demonstrate in the blood of one of *von Gierke's* patients, even some days after death, a rather important quantity of glycogen, and we, also, found an increased glycogen content of the blood in our patients. Since then many investigators have reported similar findings.

In the glycogen-fattening of animals it appeared that the glycogen content in the blood was increased to a notable degree, compared with the normal animal values, the younger the animal, the greater the elevation, and the earlier this elevation occurred. When the fattening continued, the glycogen content of the liver decreased, the content of fat increased and the glycogen content of the blood decreased until it was lower than the normal values, this decrease was greater, the younger the animal. This transition from increase to decrease of the blood glycogen should thus speak in favor of transition of glycogen into fat. This point might have some significance for the differential diagnosis between glycogen liver and fatty liver.

In connection with these animal experiments a short remark on glycogen in the urine is not out of place.

Capppenberg in 1931 was of the opinion that he had established the fact that glycogen often occurs in small quantities (to 0.1%), sometimes in larger quantities (to 1%) in human urine. We thought that this could have a diagnostic significance in glycogen disease, especially when there was a localisation of the condition in the kidney as found by *von Gierke* (nephromegalia glycogenica). We were not successful in demonstrating glycogen in the urine of our patients, using the method of *Capppenberg*.

In the meantime these findings of *Capppenberg* could be confirmed neither by *Junkersdorf* and *Mischnek*, nor by *Schulz* and *Becker*. The first-mentioned investigators came to the conclusion that what *Capppenberg* thought to be glycogen, was in reality not glycogen. Further, they examined a

large number of normal and pathological urines of man and dog for the presence of glycogen, but with negative result, nor could they succeed in the case of animals with an increased glycogen content of the blood. They were unable, however, to examine the urine of a patient with nephromegalia glycogenica. Although we are not justified in having great expectations in view of these negative findings, we must remember the possibility that the recognition of localization of glycogen disease in the kidney may be supported by examination of the urine.

d General symptomatology

In 1929, *Von Gierke* and *Schönheimer* published their articles on glycogen disease and in 1928 we gave the first clinical discussion of it. Since then great interest has been aroused in this morbid picture, as is indicated by the review which we have just completed of the published case reports of certain and probable examples of glycogen disease with special localization in an enlargement of the liver.

The combination of pronounced enlargement of liver and kidneys, due to the accumulation of glycogen, as found by *von Gierke*, has until now been observed only in a few cases. As a rule only very marked enlargement of the liver existed. There was sometimes a more or less marked enlargement of other organs beside the kidneys. Never did enlargement of the liver and of the spleen exist at the same time, however (though in the beginning the enlarged left lobe of the liver was thought to be an enlarged spleen), a fact of great importance in the differential diagnosis. Later on we shall come back to the enlargement of organs other than the liver through the accumulation of glycogen.

Departures from the normal in the endocrine organs in cases which came to autopsy were not constantly found, and, if found, they varied in character (hypoplastic adrenals in one of the cases of *von Gierke*, abnormalities in a few islets of Langerhans in the cases of *Unshelm* and of *Faber*, and abundant and generally large islets in one of the cases of *Krakower*). *Krakower* laid stress upon the considerable depletion of the lipoids of the adrenal found in two of his cases and analogous to that described in diabetic lipemias by *Goldzieher*.

The cases of glycogen disease in which the enlargement of the liver

was the outstanding feature all showed great resemblances, and at the same time points of difference. We shall go into this more deeply later on, but would like to make one remark first.

The question whether all the cases of glycogen disease with enlargement of the liver which have been described as such, are in reality true cases of that disease, cannot be answered with certainty. Properly speaking, one would be justified in considering as true cases only those in which either a biopsy of the liver, or autopsy confirmed the diagnosis. There are some investigators who insist upon this requirement. From the very first we have not agreed with them. An exploratory laparotomy in these patients is in our opinion not justified. Everything must be done in order to augment our knowledge of the *metabolism of these children, and thus to arrive at a well-founded differential diagnosis from other affections of the liver*. This was our position at the beginning. In many of the cases which have been published, however, there is no suggestion of a more or less extensive examination of the metabolism. Often the probable diagnosis of hepatomegalia glycogenica was founded on the clinical aspects of the case and the results of only a few studies of the metabolism.

In all cases the extraordinary *hepatomegaly* causing excessive protrusion of the abdomen is the outstanding feature. Palpation of the abdomen never causes any pain, the surface of the liver is smooth and the liver itself is firm. In many cases it cannot be ascertained at what period of life the hepatomegaly had arisen. In rare instances it was already present at birth, as a rule it was noticed after the first months of life, sometimes after the first year of life, and, when present, it progressed rapidly. In a classical case the abdomen as a whole is very distended and on the upper part of the wall of the abdomen a fine network of veins is visible. In none of the cases was a true *caput Medusa* visible, with the exception of the cases of *Exchaquet* which diverged from the usual, also, in other respects. The protrusion of the abdomen is caused by a very pronounced enlargement of the liver which as a rule occupies the whole right half and the greater part of the left half of the abdomen. In some cases the impression was obtained that after several years, rarely earlier, the liver had somewhat diminished in size, greater experience on this point is required, however. In a single case (*Worster-Drought*) the liver

after many years was no longer enlarged at all. The same holds true for the case of Parnas and Wagner, the one which finally became a case of diabetes mellitus.

Symptoms of infantilism such as retardation in growth (stature and weight) were not lacking in the well defined cases in which the condition had existed for some years. The type of the disturbance in growth varies. Some investigators (*Hertz, Unshelm*) have undertaken to analyze it but have proceeded from different premises. On the one hand, a parallelism has been drawn with the disturbances in growth such as occur in other affections of the liver and such as are generally present in chronic diseases of important organs in childhood (kidney, heart, intestine, and so on), that is, the varying forms of infantilism. According to this conception the infantilism noticed in cases of glycogen liver is a typical example of the hepatic infantilism originally described by *Lereboullet* and other French investigators. On the other hand, the disturbances in growth in glycogen disease have been put in a different category, i.e., under the conception of a dystrophy caused by a prolonged lack or shortage of carbohydrates in the metabolic mixture (*Hertz, Ellis*).

An important increase in length and skeletal development (wrist bones), as observed in both our patients within a period of some years (see below), has also been found by other authors. The cause of this amelioration is still uncertain (diet (?), hormone preparations (?), spontaneous amelioration at the approach of puberty (?)).

Many of the patients show *adipositas*. The partition of fat in these children is irregular. Face and trunk are often rich in fat, whereas the extremities, especially the lower ones, often appear to be poor in fat. By the combination of disturbance of growth arising at an early age, and the peculiar distribution of fat we can explain the characteristic habitus of many of these patients, that is, the relatively large head with a full fat face, the trunk rich in fat and the slender extremities. No agreement exists as to the explanation of the special partition of fat which is often present.

The psychic development is normal as a rule. Contrasted with these cases there have been described others in which this mental development was clearly disturbed. Not rarely the occurrence of the liver enlargement in these cases was preceded by a series of symptoms

which might point to an encephalitis, and which might be of interest from an etiological point of view

Aspect of an endocrine disturbance Undoubtedly many patients with their relatively large heads, flabby faces, disturbance of growth and peculiar distribution of the subcutaneous fat greatly resemble patients with an endocrine disturbance. Indeed our first patient and the one of *Biedermann* resembled a patient with dystrophia adiposo-genitalis. In other cases (see *Hertz*, also *Anderson* and *Vickery*) the picture was more that of a primary neuro-hypophyseal disturbance

Most of the cases of glycogen disease and more especially of glycogen liver described up to the present occurred as isolated examples. There are, however, some in which the condition had a *familial character* or in which familial incidence seemed likely. Reports on glycogen disease (-liver) in several members of one family are given especially by *Exchaquet*, and by *Ellis* and *Payne*, a familial character was further highly probable in the cases of *Bellingham Smith* and *O'Flynn*, *Unshelm*, *Warner*, and *Worster-Drought*. Evidence of a familial character of the disease existed also in some cases of glycogen heart (see chapter 3). In this connection we also remind the reader of the cases described by *Debré* and co-workers. Consanguinity of the parents of patients suffering from glycogen disease existed in our first case of glycogen liver (father and mother were cousins), and in the cases of *Unshelm* (both grandmothers of the patients were cousins). *Ellis* and *Payne* mention a case in which father and mother of the patient also were cousins.

Considering the central place of the liver in carbohydrate metabolism it is no wonder that when glycogen liver is present, disturbances in carbohydrate metabolism predominate.

Hypoglycemia and ketosis Both of our patients, while in the fasting state, showed hypoglycemia combined with ketosis. In most cases this hypoglycemia had been found to exist to a greater or less degree without the occurrence of so-called hypoglycemic symptoms. In some cases, however, convulsions or epileptiform seizures disappearing after the intake of glucose were noticed, we observed and others reported symptoms of hunger for carbohydrates manifested as great preference for a diet rich in carbohydrates (bread, potatoes), often

there was a large appetite and an inclination to take frequent meals. The patients often tired soon after exertion. In addition there was in some instances *nausea* and *vomiting* as well, the latter condition sometimes occurring in attacks of "acetonemic vomiting", especially in the morning. Recently this last-mentioned complex of symptoms has more often been regarded as connected with insufficient ability to mobilize the glycogen of the liver.

In both our cases *ketosis* existed in the fasting condition, more pronounced in the boy (in whom acetone was often found in the non fasting urine as well) than in the girl. In other cases of glycogen disease the *ketonuria* was marked or slight, sometimes even absent. The odor of the breath often demonstrated the presence of a *ketosis*. The speed and intensity with which the *ketosis* arose after a period of fasting varied greatly in those cases examined from this view point. After the ingestion of different carbohydrates an existing *ketosis* in some cases was persistent and even increased, whereas the blood sugar level rose.

The fact that the combination of hypoglycemia and *ketosis* was found in cases of glycogen disease, has overthrown the older conception that *ketosis* must be a symptom of the poverty of the liver with regard to its content of glycogen.

To give an explanation for the greatly varying conduct of the *ketosis* in the various cases examined is difficult. Prior to some years ago the following explanation seemed to be the most reasonable one. Under pathologic conditions the degree of a *ketosis* is generally determined by the ratio of glycogen to fat present in the liver. The production of ketone bodies grows as the glycogen deposit decreases and as the fat deposit in the liver increases. In glycogen disease the glycogen in the liver behaves essentially as if it were not available for combustion. Which part of the glycogen can be burned is unknown. The ratio of glycogen to fat in the liver in these cases, as autopsies have taught, varies greatly.

The more carbohydrates are available for combustion, the more difficult it is to provoke *ketosis* in a fasting condition. The fact that in children with a glycogen liver pre-existing *ketosis* continues for a long time after the ingestion of carbohydrates, or in the beginning is even intensified, points to the existence of a disturbance in the inter-

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pressed as acetone was 20.4 mgm per 100 cc, against a normal value of 0-3 gm. The urine of the same period gave only a weakly positive acetone reaction. In our opinion the absence of acetonuria in the fasting state in some cases of glycogen liver does not on these grounds diminish the significance of the ketosis for the recognition of this disease. Though we recognize the practical objections involved, an investigation of the degree of ketonemia is obligatory in these cases before one is justified in excluding absolutely the presence of a ketosis.

The following arguments must be considered in regard to the possible significance of hormonal factors in the occurrence of varying degrees of ketosis in cases of glycogen liver, other than a possibly diminished production of insulin or of thyroid hormone. Clinical symptoms and the results of experiments on metabolism in different cases of glycogen liver point to a possible connection with a disturbed hypophyseal function. We shall go into this subject more deeply elsewhere. The question here is whether in glycogen disease the ketosis may also be related to pituitary factors, more especially to an overproduction of the so-called ketogenic hormone. In this connection we mention only two points which in our opinion make this explanation improbable. 1. In animal experiments with the blood and the urine of our boy—who showed the strongest ketosis and presented, moreover, the aspect of a patient with dystrophia adiposo genitalis—Dr. Dingemans could not find any proof for the above mentioned conception. 2. A minor argument. The clinical symptoms and different peculiarities in the metabolism in different cases of glycogen liver in general point more to a hypo-production than to a hyperproduction of the pituitary hormones, with which the ketogenic hormone is associated.

Of great importance in the differential diagnosis may be the remarkable fact that in some cases of *congenital steatosis of the liver*, which both clinically and with respect to the metabolism greatly resembled glycogen liver, acetonuria was not present (Debré and co workers, Kramer and co workers), even under conditions when in glycogen liver acetonuria may occur in a marked degree (after ingestion of hydrates, after injection of adrenalin).—This point is of great importance, as in the opinion of different authors the differential diagnosis between cases of glycogen liver and such cases of fatty liver

mediary carbohydrate metabolism —In this regard there is an analogy with the corresponding disturbance which has been demonstrated by many investigators (*Akerrén*) in children, adults and in animal experiments after a prolonged use of a diet poor in fat

In addition to this liver factor there are other factors to be reckoned with in explaining the varying ketosis in glycogen disease, namely the *diet* of the patient, the condition of *kidneys* and *muscles* and, as recent studies have taught us, very probably also *hormonal factors*. It is not necessary to dwell here on the significance of the diet for the degree of the ketosis. The eventual rôle of the kidneys and muscles in the genesis of a ketosis in cases of glycogen disease requires further interpretation. It appears clearly from the researches of *Snapper* and *Grunbaum* that under normal conditions the production of ketone bodies takes place in the liver, and their destruction occurs in the kidneys and muscles. Under normal conditions production and destruction are approximately balanced. A marked ketosis can arise either by an increased production of ketone bodies in the liver, or by an insufficient destruction of ketone bodies in the kidneys and muscles, or by a combination of both factors. Since *von Gierke* has described the combination hepatonephromegalia glycogenica, one has to bear in mind that in cases of glycogen liver glycogen may also be accumulated in the kidneys, eventually accompanied by enlargement of these organs. Analogous to the condition in diabetes mellitus certain intermediary functions of the kidneys, of which the destruction of the ketone bodies is one, may be changed by this accumulation of glycogen and the enlargement of the organ. The same principle may hold true for the rôle of the muscles in the destruction of the ketone bodies, now that their share in the accumulation of glycogen in glycogen disease has been repeatedly established.

Here we wish to recall that the determination of the ketone bodies in the urine does not give a true indication of the metabolism of these bodies. As there is no definite level for the excretion of the ketone bodies by the kidneys, a hyperketonemia may exist without hyperketonuria. The opposite also holds true —As an illustration, the following findings may be mentioned here: recently a determination was made of the ketone bodies in the fasting (venous) blood of one of our patients. The value obtained for the total ketone bodies ex-

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would be very difficult. The fact that acetonuria was never found in a case of fatty liver such as that described by *Kramer* and co-workers—in which at the autopsy no glycogen at all was found in the liver—very probably indicates that the ketogenic functions of the liver are disturbed in such cases. This absence of ketosis in cases of congenital steatosis of the liver deserves attention, the more so because even in cases of glycogen liver where next to glycogen also much fat was found in the liver, there did exist a ketosis (cases of *Krakower* and probably our first patient).

The ketone bodies are the products of the beta oxidation of fats. Next to a beta oxidation, there also exists, however, an omega oxidation of the fats, described by *Verkade* and co-workers. It has never yet been determined whether products of this omega oxidation of fats occur in the urine of patients with fatty liver.—In the urine of our patients with glycogen liver products of this oxidation were absent.

Disturbances in fat metabolism and its endocrinal control can be studied by examining the ketonemia after a fat-meal much better than by the determination of the ketonemia in the fasting state (see the recent publication of *Kauvar*)—Comparative study of the ketonemia after a fast, and—what appears to be of greater value—after a fat-meal, in cases of glycogen liver and in cases of fatty liver, would be of the utmost value for our insight into the metabolism of those cases, and for the differential diagnosis. Such a study would also help us in finding possible relations between both conditions, as *Debré* suggested.

The *blood sugar curve* after the ingestion of glucose was nearly always abnormal in the cases examined, but the type of the curve varied greatly. In both of our patients we found a so-called biphasic curve, which was also obtained in some other cases. The blood sugar remained increased for a longer time than normally, the maximal rise, however, was not very marked. No glycosuria occurred. In other cases the elevation was greater, so that a more or less diabetic curve with sometimes greatly increased blood sugar was obtained, the increase took place more slowly and at a later time and lasted much longer than normally. Flat curves have been seen in some cases, with absence of hypoglycemia in the fasting condition.—The explanation of these different curves is not as simple as some authors indicated.

when they gave as their opinion that the long-lasting and marked increase in blood sugar could be explained by the difficulties of storage of the circulating sugar alone, owing to the enormous accumulation of glycogen in different organs. Here, also, other factors (rôle of the kidney) will have to be considered.

With a single exception the experience is that the tolerance for glucose is not decreased in glycogen liver even after giving large amounts of this sugar, and notwithstanding a very important rise of blood sugar. Only in a few cases was a slight glycosuria observed after the ingestion of glucose. The case of *Parnas* and *Wagner*, as mentioned before, was noteworthy in this respect. Also a case like that of *Thoenes* which is sometimes reckoned with the cases of glycogen liver, exhibited a peculiar behavior in this regard, since the hyperglycemic curve after ingestion of glucose ended in five hours with hypoglycemia, collapse and the excretion of acetone in the urine.

The effect of adrenalin. Most investigators have contented themselves with determining whether an important elevation of the blood sugar always followed the injection of adrenalin. As a rule, as in our patients, only a small elevation occurred, but *in some cases the result was almost that encountered normally*. Formerly we should have concluded from the absence of any important increase in the blood sugar, that no glycogen deposit which could be mobilized was present in the liver or in the muscles. Since the report by *Wilder, Allen, Power* and *Robertson* of a patient with hyperinsulinism we know that no rise of the blood sugar need follow after the injection of adrenalin. The *Coris* have furthermore tried to demonstrate that the elevation of the blood sugar which normally occurs after adrenalin injection is only partly caused by mobilization of liver glycogen, and this only in so far as the primary elevation is concerned. The adrenalin hyperglycemia should be based chiefly on a decreased consumption of glucose in the muscles.—This conception of the *Coris* was recently criticized by *Soskin, Priest* and *Schulz*. If the opinion of the *Coris* should prove to be right, then we can say that in speculating on the existence of a glycogen depot in the liver which can be mobilized, stress must be laid on the non appearance of the initial elevation of the blood sugar. In judging this adrenalin effect in cases of glycogen liver, sufficient attention has not always been paid to this initial

elevation In those cases where due attention has been given to it, this initial elevation has been slight, though not constantly so No glycosuria was ever seen The absence of this initial rise of the blood sugar has, however, also been established in those cases where the liver certainly did not contain glycogen, namely in cases of fatty liver *Kramer* and his co-workers, for instance, obtained in their patient the following results fasting sugar 28 mgm %, 10 minutes after injection of 12 minims of adrenalin 26, after 20 minutes 28, after 40 minutes 20 and after 60 minutes 21 mgm % From these results doubts have arisen as to the significance of the adrenalin test in glycogen liver

However, some other deviations from the normal in the adrenalin test will probably enable us to differentiate a fatty liver with its aid Thus we may mention, in the first place, the important increase in the ketosis after the injection of adrenalin, as noted in patients with glycogen liver with ketosis Further, it has been found repeatedly that acetonuria, although absent before the injection of adrenalin, was present after injection In normal persons this effect does not occur at all, or only to a very slight degree In the patient of *Kramer* and co-workers, who had a fatty liver, no acetonuria was present after the injection of adrenalin

It may be worth mentioning that while performing this adrenalin test in our boy an attack of vomiting occurred which began at the moment when the marked excretion of ketone bodies was at its highest Such an attack of vomiting, which quickly disappeared after the ingestion of carbohydrates, gave the impression of being similar to an attack in a patient with recurrent vomiting Formerly such attacks occurred spontaneously in our boy We have connected these attacks with an increased burning of fat occurring in a condition of defective glycogenolysis Furthermore, we have called attention to the possible significance of this (temporary) defective glycogenolysis as an explanation for the attacks of recurrent vomiting in general In the extensive literature on cyclic vomiting in childhood this point has often been considered of late

The adrenalin effect was found in some cases to be abnormal in that the rise of the lactic acid content of the blood, which normally accompanies the hyperglycemia after adrenalin injection and which

is related to an increased splitting of the muscle glycogen, was only very slight or absent (*van Creveld, Lindsay* and co-workers)

Furthermore, in combining the subcutaneous injection of adrenalin with the oral administration of glucose in an amount ordinarily used for the tolerance test, an abnormal result (*Burkens*) was obtained in both our patients

Summing up these arguments, it seems to us that in diagnosing a glycogen liver great significance must be attributed to the adrenalin test, provided that the procedure is not restricted to the determination of the blood sugar curve. For the differential diagnosis from fatty liver, special attention must be paid to the existence of a ketosis, or to the tendency for such a ketosis to arise. If in the fasting condition a marked ketosis is present, then the adrenalin test is very probably superfluous, and if performed at all, it should be carried out very cautiously.

The vasomotor symptoms following the injection of adrenalin were normal in cases of glycogen liver.

Insulin effect An important point is the sensitivity of patients with glycogen liver to small amounts of insulin, as first found by the author. The effect was studied by several investigators (*van Creveld, Loeschke, Hertz, Rauli* and *Zelson, Sundal*). *Rauli* and *Zelson*, after 2 units of insulin, found only a moderate reduction of the blood sugar, after 5 units, however, a long lasting reduction of the blood sugar was noted (initial value 60 mgm, 15 minutes after injection 70 mgm, 30 minutes after 55 mgm, one hour after 45 mgm, 3 hours after still 35 mgm), without shock symptoms.

The sensitivity to small amounts of insulin, such as is met with in glycogen liver, may be related to a liver function modified as regards the carbohydrate metabolism, or it may have a neuro-hormonal origin. This sensitivity has been found, on the one hand, in severe liver lesions, on the other hand, when the contra insular hypophysis hormone is lacking (sensitivity to insulin found in hypophysectomized dogs, in cases of *Cushing's* basophil adenoma), or when the adrenal medulla is destroyed (*Britton* and co-workers, *Harrop* idem). In severe liver lesions the sensitivity is very probably related to the hypoglycemia, which so often is present, and the failure of a glycogen depot. In glycogen liver we may say that both factors are present,

since the glycogen depot behaves for the greater part as if it cannot be mobilized. Information as to how far the sensitivity to insulin is related to such peripheral factors, or to neuro-humoral factors, must depend on the results of further investigation.

The presence of the *so-called initial insulin-hyperglycemia*, which, when present, would prove the existence of a glycogen depot, was studied by the author and by *Hertz*. The effect is not produced by pure insulin preparations. In our girl no such hyperglycemia was noted and in *Hertz*' case the effect was doubtful. The absence of the effect in itself proves either the absence of a sufficient glycogen depot, or—as is the case in glycogen liver—the presence of a glycogen supply which can be mobilized only with difficulty.

Galactose and fructose test. Tests with galactose to examine the liver function gave normal values, even in cases with marked ketosis. This fact is more or less in contradiction to the decreased tolerance for galactose (and fructose), if the food is lacking in carbohydrate. This phenomenon has been found by some investigators in normal people. Tests with fructose in the cases examined also gave normal figures for the most part. Abnormal blood sugar curves after fructose have been obtained, especially by *Ellis* (initial marked rise of blood sugar).

Glycogen of the blood. We paid special attention to the glycogen of the blood after *Schonheimer* had found much glycogen in the blood of one of *von Gierke*'s patients 6 days after death. In both of our patients we repeatedly found, by means of a micro method of our own, increased values, as compared with the values in the great majority of the control cases. This increase is principally caused by an increase of the glycogen in the blood cells. Further we found that the blood glycogen in glycogen disease was split with greater difficulty than under normal conditions, whereas glycogen added to the serum of our patients was split in the normal way. *Beumer* and *Loeschke* say that in the blood of their patient, kept sterile, the blood glycogen could be split to a greater degree than under normal conditions.—The increased values for the blood glycogen have been established by several other investigators, also (*Beumer* and *Loeschke*, *Hertz*, *Sundal*), but this increase was found in conditions other than glycogen disease as well (*Ellis* and *Payne*). In two cases (*Schall*, *Rauh* and *Zelson*)

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no glycogen at all was found in the blood of the patient! It may be that the method used played a rôle, a closer study is certainly required. In the two cases of *Anderson* the glycogen in the blood was determined following an acute infection, and then no increase was found—In the opinion of *Ellis* and *Payne* the increase of the blood glycogen in glycogen disease is due to an increase of glycogen in the red cells and this fact should support the clinical findings which indicate that in this disease many groups of cells other than the liver cells are also affected.

Unshelm who recently made an extensive study of the glycogen in blood, found a parallelism between glycogen content of the blood and the number of leucocytes. He could give no complete explanation for the stability of blood glycogen. However, the author concludes from his experiences, that the stability of the glycogen, as found in the liver in one case of glycogen disease, differs from that of the glycogen in the blood. *Staub* and *Golandes*, who recently studied the glycogen of the blood extensively, lay stress on the fact that each individual has his own constant fasting value.

No doubt the study of the glycogen of the blood will keep its interest in the further research work on glycogen disease. The studies of *Willstätter* and *Rohdewald* (compare later on) on the blood amylases and the condition of glycogen in the leucocytes will probably play a great rôle in this part of the research work on this disease.

Water metabolism. In view of the important place of the liver in the water metabolism it is no wonder that these patients with their enormous enlargement of the liver repeatedly showed disturbances in the water metabolism (*van Creveld*, *Wilder*). That the large deposit of glycogen should also contribute to an increase of the water content of the liver was a correct supposition, for so it has appeared from the results in some cases which came to autopsy. Based on the results of *Bridge* and *Bridges*, the existence of a mathematical relation between liver glycogen and liver water must be regarded as being highly improbable, however.

Cholesterol in the blood. As a rule the total cholesterol content of the blood was found to be more or less increased in the cases examined. There were, however, a few exceptions. It appeared to us and to a few other investigators that the ratio of cholesterol to cholesterol

ester was as a rule nearly normal. A marked decrease or even total disappearance of the amount of cholesterol ester in the serum, such as is found in chronic parenchymatous liver affections, was lacking in these cases. The fact, that the increase in the cholesterol content was not present in two cases of congenital fatty liver may be of some significance from the standpoint of differential diagnosis. To what this increase in the cholesterol content must be ascribed is not yet clear.

Lipemia Various investigators have been struck by the milky appearance of the blood serum of their patients. In determining quantitatively the cholesterol it appeared that in addition to this substance the total fat content was, also, increased to a considerable extent. *Beumer* and *Loeschke* found in their case that after giving an extra supply of fat by mouth the content of the serum in total fat and in cholesterol increased and that this increase lasted much longer than would normally have been the case. This fact should be of significance in the differential diagnosis from liver cirrhosis, since in liver cirrhosis any lipemia after an extra supply of fat by mouth should be totally lacking as consequence of disturbances in absorption (*Bürger* and *Habs*). The fact could not be confirmed in one of the cases of glycogen liver, described by *Harnapp*—The value of this test for the differential diagnosis of different liver affections has, moreover, of late been called in question. The lipemic curves in patients with liver disease during a prolonged period of fasting, and after extra fat has been given by mouth, very often did not show deviations from normal curves (*Leites* and co-workers).—The increase of cholesterol was not infrequently absent in patients with a normal cholesterol metabolism just as in those with an abnormal one (*Snapper* and *Parisel*).

Protein partition of serum In both of our patients the protein spectrum of blood plasma was practically normal. In particular the very important increase in the globulin content of the serum, which is present in the majority of chronic parenchymatous liver affections, was found to be absent in both of our patients on repeated investigation. In judging the globulin content of the serum the deviations in this content occurring after birth, must be considered. This fact has been overlooked by *Harnapp*—In both of our patients corre-

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sponding to the normal protein spectrum of the plasma was the normal sedimentation rate of the erythrocytes in the defibrinated blood, well as in the non-defibrinated blood. The Takata-Ara reaction, flocculation-test which is nearly always positive in chronic parenchymatous liver affections, was negative in our boy and only weakly positive in our girl.

In the case described by *Hertz* the sedimentation rate of the erythrocytes was markedly increased and the fibrinogen content markedly decreased, so that probably there did exist an increased globulin content. This is a very peculiar finding, in this case, in which other liver function tests employed gave almost normal results. (See in this connection, also, the cases of *Exchaquet*.)

Urobilinuria was absent in the great majority of the cases. The urine of our girl showed a slightly positive reaction for urobilin, the same was found in some other cases.

Other liver function tests Several authors have made use of liver function tests other than those mentioned above. No impairment of hepatic function was found with the aid of such tests.

The basal metabolism was rarely determined. In both of our patients and in one of the patients of *Schall* and *Harnapp* it was slightly increased. The patient of *Hertz*, however, showed a very greatly increased metabolism.

Blood normal bleeding-time, normal coagulation time and normal numbers of platelets have been reported. The fragility of the red corpuscles was normal. The number of leucocytes in the uncomplicated cases varied. For the most part a slight leucopenia with relative lymphocytosis was encountered. In our first patient (boy) the number of leucocytes was usually low, once as low as 2900. In our second patient (girl) the number of leucocytes was normal or slightly increased. In other cases the number of leucocytes was normal or slightly increased, only once was it found to be greatly increased (*Beumer and Loeschke* 24 800). The number of eosinophils not rarely was increased to 5% or more. In several cases a mild anemia was found with normal or slightly decreased color index, and now and then a few nucleated red cells in the blood film. The van den Bergh reaction, both direct and indirect, was nearly always negative, icteric index not increased.

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A *slight temporary jaundice* was occasionally mentioned in the histories

The chlorine in total blood and serum in our cases and in those of *Ellis* and *Payne* was normal *Hertz* found hypochloremia

No changes were found in the calcium or the magnesium of the serum, or of the serum filtrate, nor in the inorganic phosphorus of the serum filtrate The inorganic phosphorus of the blood was decreased in cases of *Ellis* and *Payne*, in one of the cases of *Biedermann* and *Hertz* and in the case of *Sundal*

The von Pirquet and Mantoux tests were negative

Serological test with the serum for lues or echinococcus were negative in nearly all cases In the case of *Beumer* and *Loeschke* the parents were luetic In the case of *Sundal* the Wassermann test during a period of jaundice was temporarily positive In the case of *Hertz* a slightly positive echinococcus reaction was obtained with the blood on one occasion, but this could not be considered as proof of the presence of echinococcus

Blood-urea nitrogen was normal

The non-sugar reducing fraction and the glutathione content of the blood were normal in both our patients

Ferment investigations in glycogen disease The greatest attention has been paid to the presence of carbohydrate splitting ferments, both during life and in the organs after death As regards the results of the latter investigations the reader is referred to the description of the cases (*Schonheimer*, *Unshelm*, *van Creveld*, *Hertz*), and to the chapter on pathogenesis During life the glycolysis of the blood was found to be normal (*van Creveld*, *Hertz*, *Sundal*, *Harnapp*)

The diastatic activity of the blood was for the most part low as compared with that of normal children (*Loeschke*, *Hertz*, *Rauh* and *Zelson*) *Unshelm* found an increase of blood amylase in the blood of his patient, taken seventeen hours after death

The urine diastase was in the main found to be greatly increased (*Beumer* and *Loeschke*, *Hertz*, *Unshelm*, *Rauh* and *Zelson*, *Harnapp*) Concerning the cause and significance of this excess of diastase in the urine there have been different opinions, without however a definite conclusion One has thought that the diastase originated from the liver, or from the pancreas, the increased excretion in the urine has

also been connected with an increased permeability of the kidneys. Whether this is related to an increased deposit of glycogen in the kidney is not yet settled.

It has recently been pointed out that a more intensive study of the organ ferments in autopsied cases of glycogen disease might be important for our insight into the cause of that condition, when the new and important investigations of *Willstätter* and *Rohdewald* are kept in mind. Those investigators made a thorough study of the ferments of isolated leucocytes and of the state of the glycogen in the liver, muscles and the leucocytes. They differentiated "Desmoamylases" which remained attached to the cell rests, but may be brought into solution by means of proteolytic ferments, and "Lyoamylases" which could be separated from the killed cell-constituents by solutions of definite pH or by glycerin. The activity of the desmoamylases may easily be arrested, conversion of desmo- into lyoamylases, however, is very probably accompanied by a highly increased activity of the amylase. To understand the splitting of glycogen in the cells, next in importance to the amylases is the condition of the glycogen itself. In the leucocytes glycogen should be attached to the cell proteins as an adsorptive or more probably as a chemical compound (compare the hypothesis of *Unshelm* on the binding of glycogen in glycogen disease in order to explain the great stability of the glycogen in this disease) — The application of these researches to cases of glycogen disease may indeed help us in solving the problem.

Lipolytic activity of the serum was normal in both our patients. In addition both a quinine- and an atoxyl resistant lipase were absent from the serum. In the case of *Solomon* and *Anderson* the lipolytic activity was decreased. In *Hertz'* case the lipase content of the serum was distinctly increased, the increase being caused principally by a quinine-resistant (liver-)lipase. The author supposes that this increase in his case is not a sign of severe liver cell damage (as is usually accepted), as other liver function tests employed gave almost normal results. Still it remains at least peculiar that along with this increase in quinine resistant lipase there existed in *Hertz'* case a hypo fibrinogenemia and, as may be inferred from the increased sedimentation rate, very probably also an increased globulin content of the serum. The latter conditions in the blood lead one to suspect cirrhotic proc-

esses in the liver, which indeed have been found by others in connection with glycogen liver (*Lindsay* and others)

The presence of much quinine-resistant lipase has, however, lost much of its value of late as a specific test for liver disease (*Hulscher*)

The *phosphatase* activity of the serum was normal (*van Creveld, Ellis* and *Payne*)

Obstipation as well as *diarrhea* and both in the same individual have been observed now and then. The investigation of the stools in the great majority of cases gave no indications at all of a disturbance in digestion or absorption. A few exceptions may be mentioned. In the case reported by *Naish* and *Gumpert* the faeces contained large amounts of starch. The much-discussed patient of *Parnas* and *Wagner* showed in an early period diarrhea, fermentation of the stool and temporary fat-stools. After giving thyroid, beside lipemia and lipuria, steatorrhoea developed. Temporary steatorrhoea also existed in the case of *Solomon* and *Anderson*.

In many cases *walking* was impaired or the patients soon became tired. The rapidly increasing enlargement of the abdomen might explain these symptoms. In others they could be explained also by a genu valgum which developed or—what is still more important—by an existing hypotonicity or poor development of the muscles of the buttocks and the legs, which also gave rise to the possibility of abnormal stretching of joints. In some patients this caused a peculiar gait, resembling that seen in certain muscle diseases (*Debré*). The neurological investigation in these cases gave a negative result.

X-ray investigation of internal organs in the majority of the cases of glycogen liver gave normal results. The heart was often pushed upwards by the enlarged liver. Only once was the combination of a very large liver and evident enlargement of one kidney found (*Wilder*).

Rontgenograms of the long bones in several cases demonstrated the presence of the well-known transverse lines in the metaphysis as a sign of irregular growth. Not infrequently a growth of the long bones could be inferred from the displacement of these lines. Histologically the lines were characterized by the persistence of transverse bony trabeculae (*Krakower*).

The development of a slender and delicate skeleton is mentioned by several authors.

Osteoporosis was noticed in the cases of *Unshelm* and *Hertz*. In the latter's case fracture of the femur from slight accidents occurred several times, these fractures healed within the normal time limits — Osteoporosis which gave rise to fractures of the femur was also present in one of the cases of *Debré* and co-workers

Our first patient (boy) in 1930, also, had a fracture of the right femur, caused by a slight trauma, there were, however, slight rachitic abnormalities of the bones as in several other cases. In the case of *Hertz* the osteoporosis predisposing to fractures was connected with a hypophyseal disturbance

The development of the skeleton of the wrist in several cases was found to be retarded for the age of the patient. However, not rarely (e.g. in both our patients) a further development of the bones of the wrist was noted within a relatively short time (see later on)

X-ray pictures of the skull rarely showed abnormalities of the sella turcica or other regions (*Wilder, Erben* and *Kuster*)

Retardation in the disappearance of the milk teeth was noticed several times (*van Creveld, Hertz, Ellis* and *Payne*)

Abnormalities in hair growth diffuse falling out of hair was noticed in some cases (*Debré*), in others, persistence of fine lanugo hair in spots or distributed uniformly. Sometimes diffuse or localized hypertrichosis was noticed (*Bellingham Smith* and *O'Flynn*). In the latter's case the skin also showed a rapidly increasing pigmentation

Hemorrhages. Our first patient (boy) during the first years of observation often had blood in the stools, not infrequently in large quantities. Sometimes only occult blood was present. In the beginning we attributed this symptom to a possible obstruction in the portal system. Later on a polyposis recti was found, which was the most likely cause of the rectal bleeding. A tendency to hemorrhage was noted during life in the cases of *von Gierke*. Several patients repeatedly had epistaxis (*Hertz, Biedermann*). Only in one case (*Hertz*) was there found a definite change in the blood which could explain this tendency to hemorrhage (fibropenia in the case of *Hertz*). Transitory purpura was present in one of the patients of *Debré*

The superficial veins over the upper part of the abdomen and the lower part of the thorax were often dilated. A real *caput Medusae* was only noticed in the cases of *Exchaquet*. In some cases telangiectases in the face were seen

Phosphate excretion after carbohydrate ingestion Close relations exist between carbohydrate and phosphate metabolism. These have been studied by many investigators. In the normal organism these relations are demonstrated by the onset of changes in the phosphate content of blood and urine after the ingestion of different sugars. When disturbances in the carbohydrate metabolism are present, these changes in the phosphate metabolism vary (*Cori, Pijoan and Quigley*). It was of interest to study these changes in glycogen disease. In order to avoid a repeated withdrawal of blood we studied only the excretion of inorganic phosphate in the urine, before and some hours after ingestion of different sugars (3 x 30 gm of glucose, 4 x 30 gm of fructose). Comparison of the results obtained in the patient with those in healthy persons shows that in the majority of the experiments a diminution in the excretion of inorganic phosphate occurred. As a rule, however, this diminution appeared later than in healthy persons and was not so marked. Contrary to what usually occurs the diminution after glucose was as a rule greater than that after fructose—After the ingestion of dioxyceton, a ketotriose, under normal conditions a marked diminution in the excretion of inorganic phosphates occurs, in our boy the excretion of phosphates showed in two experiments almost no changes under these conditions. The possible significance of this fact we have discussed elsewhere—As regards the excretion of inorganic phosphates after the ingestion of glucose and fructose, our results speak in favor of the conception that phosphates are bound to carbohydrates, but the duration and the rate of excretion differ from that found in normal persons. We cannot deduce anything more from these results.

Hertz examined the changes in the excretion of phosphates in the urine on one occasion after 30 gm of glucose, and on another after 30 gm. of fructose. Both times he found a greatly increased excretion of phosphates, as we usually see in diabetes mellitus.

The remark has been made that the relatively decreased phosphate excretion found in our sugar tolerance test might correspond to the delayed return to normal of the blood sugar. It appears that in this regard, also, no definite conclusions can be drawn. For example, after giving 30 gm of fructose, *Hertz'* patient had a normal blood sugar curve, but a highly increased phosphate excretion. Our patient had an abnormal blood sugar curve after fructose, but the phosphate excretion was for the most part less than normal—*Harnapp* after giving 30 gm of fructose and of galactose found a slightly increased phosphate excretion in the urine, after giving different amounts of glucose the results were inconstant.

On the basis of recent investigations we came to the conclusion that if

one wants to draw inferences from the changes in the phosphate metabolism after the ingestion of sugars in patients with glycogen disease, a simultaneous examination of the phosphates of the blood, perhaps even of the different fractions of the blood phosphates, is imperative. We do not underestimate the practical difficulties of the repeated withdrawal of the rather large quantities of blood necessary for the examination of this phase of the problem.

Respiratory quotient In the introduction we pointed to the difficulties which one encounters in judging the variations in the respiratory quotient which have been found by recent investigators. Almost always we have to deal with the resultant of different processes which take place simultaneously. With this qualification we shall report at this point some of the results obtained in glycogen disease.—In our first patient we found normal values for the R.Q. (0.725, 0.775) in the fasting state. After the ingestion of 25 or 50 gm. of glucose this R.Q. rose during the first hour, the maximal elevation was reached after two to three hours, which is somewhat later than usual. During each observation period of four hours in four experiments we never found an elevation of over unity. Only once did the elevation really reach 1, namely two and three quarters hours after the ingestion of 50 gm. of glucose. In the patient of *Wilder* with hyperinsulinism the R.Q. rose immediately and reached the maximal value of 1.06 after two hours, after two and three quarters hours it still was 1.04. In *Schall's* cases the R.Q. was increased after the tolerance test with glucose, after two and after four hours it was still increased, but its value did not rise higher than unity. In the patient of *Parnas* and *Wagner* the R.Q. remained about the same during the first hours after ingestion of glucose, after three hours it rose above unity (*Helmreich* and *Wagner*). *Wagner* at that time thought that this fact could only be explained by a conversion of sugar into fat. In our second patient (girl) the R.Q. after the ingestion of 20 gm. of glucose rose in one hour to higher than unity, but the girl had not kept quiet during the observation. A second attempt at determination likewise did not succeed.

The changes found in the R.Q. of our first patient after the ingestion of glucose were about normal, thus differing from those in diabetes mellitus. On the basis of these findings and the changes observed at the same time in the blood (blood sugar) and in the urine (disappearance of the ketosis), we offered as the most probable explanation the hypothesis that in our patient after the ingestion of glucose there does occur a fixation of glycogen, but accompanied by a slow combustion of sugar.

The R.Q. in our first patient after the ingestion of *fructose* rose slowly,

during the first hours in two experiments (normally a quick rise to even greater than unity) The possibility that a difference in the speed of absorption might have played a rôle here cannot be excluded It was more likely, in our opinion, that our patient was able to fix fructose (as glycogen?), but that the quantity of sugar which was oxidized was smaller than after the ingestion of glucose (compare in this connection the phosphate excretion after fructose and after glucose)

We also studied the changes in the R Q after giving a ketotriose, dioxyceton, especially known as a substance capable of forming liver glycogen, and also as a recognized anti-ketogenic substance Normally after dioxyceton the R Q rises quickly to unity and even higher In our first patient the rise of the R Q was only small An effect on the excretion of ketone bodies, however, was distinctly noticed after one hour, whereas the marked decrease in phosphate excretion which normally is present after dioxyceton ingestion, failed in our patient —Thus on the one hand, we found changes in the R Q which greatly resemble those occurring in healthy people (after glucose), on the other hand, the changes were only slight, whereas normally they are considerable (after fructose and dioxyceton) We are not justified in concluding from the last-mentioned findings that in our case, after giving fructose or dioxyceton, only glycogen formation takes place, as there is also a distinct effect (appearing later) upon the ketosis, e g an important oxidation of sugar

It is accepted that the formation of glycogen from various sugars is influenced by several factors To these factors belong, amongst others, the rate of absorption from the intestines, the chemical configuration of the sugar molecule, the sugar concentration in the blood, insulin and epinephrine (*Cori*) The rate of intestinal absorption in our experiments and in those of others with different sugars remains unascertained This fact of itself makes it difficult to draw further conclusions

Note

The following reports have come to our attention since this paper was originally prepared

Linneweh has recommended the use of dihydroxyacetone for the differential diagnosis between liver cirrhosis and hepatomegalia glycogenica In glycogen disease the application of this ketotriose would not give rise to the appearance of even traces of this substance in the blood, whereas in liver cirrhosis a higher concentration than usual should be found Dihydroxyacetone was determined in blood after the method of *Campbell* The value of this test will depend on a larger experience

Linneweh, who like others assumes that in "glycogen liver" there exists an increased adsorption of diastase to the cell surface, by which the enzyme activity is inhibited (diastase-glycogen), ascribes this strong adsorption and the glycogen accumulation to a certain degree of hyperinsulinism. From perfusion experiments in frogs *Linneweh* concluded that this intensified adsorption could be displaced by capillary active substances. This led to the regular oral administration of a cholic acid preparation (compound of cholic acid and lecithin) to a patient with "glycogen liver". The circumference of the abdomen of this patient decreased during an observation time of three months. During a preceding period in which the same patient was on an acidotic diet (rich in proteins) the circumference of the abdomen had increased a good deal.

Rohleder found that the excretion of ketone bodies in a patient with glycogen disease (complicated by xanthomatosis) from *Beumer's* clinic (Göttingen)—determined daily during short intervals—showed a constant rhythm. During night and in the afternoon the excretion was smallest. The rhythm maintained itself when food was withdrawn or when the excretion of the ketone bodies was fortified by a preparation of the adrenal cortex or of the anterior hypophysis. The relation to the studies of *Forsgren* and others on the rhythm of the liver functions is mentioned.

Esser and *Scheidegger* described a case of glycogen disease from the clinic of *Wieland* (Bazel). During the short time of clinical observation the patient, a girl seventeen months old, in addition to a greatly enlarged liver, osteoporosis and acetonuria, showed greatly accelerated respiration, severe perspiration, further increased residual nitrogen content and decreased chlorine content of the blood. The fasting blood sugar was normal. The girl died with symptoms of hepatic coma. At the autopsy the size of the liver appeared to correspond to that of a girl of ten years. The liver contained much glycogen and also much fat. The liver cells had a plant like structure as has also been found in other cases of "glycogen liver". Next to the liver the pancreas, kidneys, adrenals, myocardium, striated muscles, brain and gastric mucosa contained much glycogen. The adrenals were hypoplastic, which might also have been a secondary symptom.

From Japan *Katoo* reported a probable case of "glycogen liver". X ray application only slightly decreased the volume of the liver.

Neuteboom recently reported a case of glycogen liver in a boy of thirteen years. The diagnosis was made in consequence of the results of a biopsy of the liver. The liver was slightly enlarged. Hypoglycemia in fasting condition and acetonuria were absent. There was no diminished response of the blood sugar to adrenalin. The cholesterol content of the blood was

normal There was no over-sensitiveness with respect to insulin A diet poor in carbohydrates and rich in fat was well tolerated during ten months, without ketonebodies appearing in the urine and this diet prevented a further increase of the size of the liver After a few series of injections with fairly large amounts of insulin length and weight of the patient increased considerably The author is of the opinion that disordered supply of the nervous stimuli may be the cause of glycogen liver, the source of faulty innervation is sought in the upper and middle part of the thoracic spinal medulla Birth injuries should play a large rôle in the rise of glycogen-disease The author reported the results of some experiments performed in rabbits in which the thoracic marrow was damaged The results of these experiments were in favor of his theory Two forms of hepatomegalia glycogenica are to be distinguished one due to hyperfunction of one or more centres in the thoracic spinal medulla, giving rise to a reactive hyperinsulinism and to symptoms such as the author's patient shows, the other due to a hypofunction of these centres causing a relative hyperinsulinism with the typical symptoms such as hypoglycemia, ketosis, diminished sensitiveness to adrenalin and so on

Beumer studied the cholesterol metabolism in a case of glycogen disease, complicated by xanthomatosis The serum cholesterol which was very high at the start of the disease, remained high after five days on a cholesterol-free diet, and remained unchanged five after days on a cholesterol diet, and then also during three months on a cholesterol-free and fat-free diet *Beumer* found the cholesterol-ester content of the serum to be independent of the diet The accumulation of the cholesterol thus appeared to be endogenous The cholesterol balance in the period of the cholesterol-free diet was negative, and positive during the period of the cholesterol-containing diet

3 CARDIOMEGALIA GLYCOGENICA

The first article by *Pompe*, soon followed by those of *Bischoff* and *Putzchar*, brought out the significance of abnormal glycogen accumulation in explaining many cases of so-called "idiopathic hypertrophy of the heart" In his histo-chemical research of the heart in a case of so-called "idiopathic hypertrophy of the heart" *Pompe* found an extraordinarily large glycogen infiltration of the heart muscle fibers Following *von Gierke*, who had called the disease in which liver and kidney were found to be enlarged on account of an abnormally large accumulation of glycogen, hepato-nephromegalia, *Pompe* called his

case *cardiomegalia glycogenica* Since then it has appeared that this enormous hypertrophy of the heart as a result of the accumulation of glycogen takes a particular place in some respects among the cases of glycogen disease In the children with hepato nephromegalia described by *von Gierke* there was no question about the absence of a pronounced hypertrophy of the heart In his first case the heart weighed 80 gm (a girl of eight years) and macroscopically it did not show any abnormality In his second case (that of a boy of nearly five years) the heart was slightly enlarged and microscopically the cells showed some fatty degeneration And also in the many patients (all children) which have been described with hepatomegalia glycogenica, including those studied by ourselves, neither clinically nor Röntgenologically could obvious abnormalities of the heart be found The electrocardiogram also proved to be normal in both of our patients In the few cases which came to autopsy no distinct hypertrophy of the heart was found In the case of *Unshelm-Kimmelstiel*, in which the liver had the enormous weight of 1600 gm, large amounts of glycogen were found in the heart muscle on histological examination, without the heart being distinctly hypertrophied In *Faber's* case of hepatomegalia glycogenica the heart was only moderately enlarged at autopsy in the fibers of the heart muscle no glycogen was found

On the other hand, in the cases of very marked hypertrophy of the heart caused by the accumulation of glycogen, only occasionally was there a simultaneous enlargement of another organ Sometimes (*Putschar*, *Antopol* and co-workers, *Humphreys* and *Kato* in cases I and II) the liver also proved to be enlarged, but never to the same degree as the heart *Hertz* and *Jeckeln*, and *Wolff* have described great enlargement of the tongue

Thus heart hypertrophy by glycogen accumulation occupies a special place, and we may speak of a special cardiomegalic type of glycogen disease as some investigators have done already Even though in this type no particular enlargement of the other organs generally occurs, nevertheless in nearly all the cases that have been examined there were found, in addition to glycogen infiltration of the heart, glycogen accumulations in nearly all the organs studied, the same state of affairs as in the liver kidney type of glycogen disease Some results and figures may illustrate these findings

In all tissues which he examined (heart, liver, kidney, pelvis epithelium, thyroid gland, striated muscle, spleen) *Pompe* found a great deal of glycogen, notwithstanding the fact that the child had died from an acute febrile disease, that the organs had been kept for some days in the cold and after that for some time in a watery solution of formalin. According to the current conceptions of the pathologists, the greater part of the glycogen should have disappeared from the organs as a result of this method of preserving them, and after a febrile illness such as this child had.

Putschar found the liver cells and the epithelium of the convoluted tubules of the kidney vacuolated with glycogen.

In the case described by *Antopol* and co-workers the formalin-fixed material was placed in absolute alcohol four weeks after the autopsy. Analyses of the heart, liver, kidney and lungs were carried out by *Pfäuger's* method. In spite of the fact that the organs had been in 10% formalin for so long a period, 3.57% of glycogen was found in the heart, 3.25% in the liver, 4.34% in the kidney and 0.32% in the lungs. The microchemical examination showed that the thymus and particularly the bloodvessels were filled with glycogen, the muscle fibers as well as the endothelium.

In the first case of cardiomegalia glycogenica described by *Humphreys* and *Kato*, the tissues had been first placed in Zenker's solution and in formalin. The tissues fixed in formalin were embedded after one week in celloidin and stained with *Best's* carmine. Subsequently this stain was applied to the Zenker-fixed tissues. Abundant glycogen was found in this way in the vacuoles present in hypertrophied muscle fibers of the heart and of the skeletal muscles, in the liver and kidney (principally in the epithelium of the medullary tubules), and on the other hand, little glycogen was present in cartilage cells, different smooth muscles, lymphoid tissue and thymus.

In their second case the histological structure of muscle fibers of the heart, of the liver cells and of the tubular epithelium of the kidney was typically changed. The presence of glycogen was proved in the vacuoles of the heart muscle fibers after the heart had been kept in preserving fluid for five months.

In their third case (published with the consent of Dr *Martina Wollstein* of New York City) the microscopic examination of liver and

heart gave about the same result as in the preceding cases. The muscle fibers of the diaphragm were also vacuolated, the epithelium of some of the renal tubules was swollen, and centers of large pale cells were present in the spleen. Glycogen was demonstrated in formalin-fixed sections of the heart, but *not* in those of the liver.

Their fourth case (published with permission from Johns Hopkins University records) was a presumptive one, because the presence of glycogen was not proved. Myocardial fibers, hepatic cells and the cells of the collecting tubules of the kidneys showed, however, a histological structure which we now are justified in calling more or less typical.

In the case recently described by *Mansens* the autopsy was performed some hours after death. The liver and heart gave a microscopical picture typical for glycogen disease (see later). Both *Best's* carmin stain and iodine stain for glycogen were positive, whereas *Best's* stain was negative when the tissue slides were first kept in the incubator under the influence of the activity of saliva for some time. The glycogen content of the heart and liver determined in pieces of the organs kept in absolute alcohol for five months was respectively 10 and 6%. A piece of the heart tissue kept in a watery solution of formalin for the same time still showed a glycogen content of 3.9%.—In the case recently reported by *Wolff* the glycogen content of the dried organs was as follows: heart 33.2%, liver 11.7%, kidney 6.95%, tongue 35.3% (see later).—*Hertz* found in the case described with *Jeckeln* the following values for the glycogen content of the fresh organs: heart 7.9%, liver 4.12%, skeleton muscles 5.47%, tongue 3.58%, kidney 1.223% (only the glycogen content of the heart was determined immediately after the autopsy).

Some years ago we were able to make chemical analyses of tissues of different organs in a second case of cardiomegalia glycogenica in a baby of six months who died from bronchopneumonia. In the urine shortly before death no acetone was found. An abstract of the autopsy report, as well as pieces of different organs, were put at our disposal by the pathologist, Dr *E. Hammer* of Amsterdam.

The autopsy was performed 24 hours after death. When not examined immediately the organs were kept frozen for the most part for some days. At autopsy the child had a length of 60 cm, was very

thin, the panniculus being nearly totally absent. Thymus small, heart greatly enlarged, the enlargement being caused by thickening of the walls as well as by dilatation of the cavities. The wall of the left chamber measured 17 mm in thickness. No abnormalities of the valves. The isthmus aortae was slightly narrowed (circumference 15mm), the aorta itself was distinctly enlarged. The lungs, especially the left one, were compressed by the large heart. In both lungs extensive pneumonic infiltration was found. The spleen was normal in size, the cut surface bulged. The remaining lymphoid tissue was only moderately developed (intestine, lymph glands). The liver was somewhat enlarged and soft, the cut surface showed no architecture. The gall bladder was filled with brownish yellow limpid bile. The kidneys were of normal size, pale and firm, the cut surface, also, was pale.

Microscopically large quantities of glycogen were found in the fibers of the heart muscle, the liver cells (especially in the periphery of the acini), primitive bundles of the striated muscles, convoluted tubules of the second order and collecting tubules of the kidneys, pulp of the spleen (especially at the border of the follicles), adrenal (especially in the *zona reticularis* of the cortex), spinal marrow, cell bodies of the ganglion cells, hair follicles of the skin, further, in the walls of vessels and in connective tissue cells of all sorts of other organs.

The following results for the glycogen content were obtained

Heart	7.97%	Muscle	9.39%
Liver	9.13%	Lung	0.034%
Spleen	1.46%	Spinal marrow	0.583%
Adrenal	1.25%	Blood (after death)	18 mgm. per 100 cc.

We compared the results with those obtained in the organs of a baby with very marked hypertrophy of both ventricles in a case of patent ventricular septum. Both babies had passed through a period of fever shortly before death.

Heart (L V)	0.055%	Spleen	0.01%
Heart (R V)	0.07%	Muscle	0.011%
Liver	0.103%	Blood (during	
Kidney	0.062%	life)	12.75 mgm. per 100 cc.

From these results we see clearly the enormous increase in the glycogen content, not only of the hypertrophic heart, but also of other organs, especially liver and muscle, in this case of idiopathic hypertrophy of the heart. In the patient with septum-defect, in whom the hypertrophy of the heart muscle was at least as marked as in the glycogen heart, only very small amounts of glycogen were found in the available corresponding organs. The same result has since been obtained in two other cases of patent ventricular septum with very large ventricular hypertrophy.

Thus it appears that in many cases of cardiomegalia glycogenica much glycogen has been found, notwithstanding the fact that death occurred after acute febrile diseases, and in spite of the fact that the organs had been kept for a considerable time after death—with a few exceptions—in a repeatedly renewed watery solution of formalin. Just as in hepato-nephromegalia glycogenica, this fact seemed *a priori* to point to a great stability of the glycogen in these cases. We examined the glycogen splitting power of the glycogen heart muscles according to a method analogous to that first employed by *Schiönheimer* and later on used by *Unshelm* in hepato-nephromegalia glycogenica. We investigated the decrease in the amount of glycogen in small pieces of heart muscle, on the one hand, after keeping them for 48 hours at 37°C, and, on the other hand, after mixing them with the same quantity of heart muscle from a patient who died from meningitis, which latter tissue contained only traces of glycogen. We obtained the following results:

Glycogen heart alone
In mixing experiment

Decrease from 7.86 to 6.74%
Decrease from 7.86 to 1.7%

Even under those conditions, so extraordinarily favorable for glycogenolysis, the glycogen in the glycogen heart showed a notable stability which, however, disappeared for the greater part when mixed with heart muscle obtained from the meningitis patient. Just as in glycogen liver, this experiment of course did not decide the question whether the stability of the glycogen was caused either by an abnormal state of this glycogen, or by the absence of a factor necessary for the destruction of glycogen.

In his case recently described with *Jeckeln*, *Hertz* has carried out

analogous experiments When kept at the temperature of the refrigerator the glycogen content of heart and liver in his case during six days showed very little decrease At 37°C and under optimal conditions for the diastatic activity (phosphate buffer of pH 6.9–6.5) the glycogen content of the heart tissue decreased in 26 hours about 50% and then remained the same

The enlargement of the heart in cardiomegalia glycogenica, as a rule, is an enormous one The weight of the heart, in comparison to the age of the patient, is much too large In the case of *Pompe* the heart weighed 190 gm (normally in the case of a girl of seven months 36 gm), in the case of *Putschar* 110 gm (four months old), in that of *Antopol* 85 gm (four and a half months old) In the four cases reported by *Humphreys* and *Kato* the heart weights were respectively 140, 260, 90 and 128 gm (the normal weights in the corresponding ages are respectively 29, 37, 27 and 31 gm) In the case reported, by *Hertz* and *Jeckeln* (40 days old) the heart weighed 45 gm (normally at that age 21.4 gm)

In the cases of glycogen heart the form of the heart has been round, the apex being formed for the most part by both ventricles The valves are normal as well as the bloodvessels originating from and going to the heart The wall of both ventricles is thickened to a high degree (e.g. in the case of *Pompe* the thickness of the left ventricle was 29 mm), whereas in adult men this is only 7–10 mm, the cut surface of the right ventricle at the conus was 9 mm, whereas in adults at that place it is only 2–5 mm —In comparison to the heart, the lungs generally seem small, especially the left lung, and more especially the lower part of this lung, which is pressed together to form a thin layer, having become atelectatic by the pressure of the enormous heart

The histological aspect of the heart in cases of idiopathic hypertrophy from glycogen accumulation is quite characteristic The cells of the heart muscle are at first sight changed beyond recognition *Pompe* gave the following description “un réseau de mailles rondes, ovales ou plus allongées, dans lesquelles il y avait souvent un noyau au centre ou hors du centre de la cavité sur le bord” High power magnification demonstrated that the network bordering the open places showed some stripes now and then, and this indicated that one

had to do with vacuolated fibers of the heart muscle. According to whether these fibers were cut lengthwise or crosswise they formed round, oval or elongated open spaces. In all of the vacuoles a strongly positive glycogen-coloring could be obtained. *Antopol* and co workers lay particular stress upon the fact that the amount of stained substance in the heart, both with *Best's* carmin stain for glycogen and with the iodine-stain, was about the same. In accordance with the investigations of *May* and *Kordowitch* the presence of significant quantities of galactogen was ruled out herewith. *Antopol* and his co workers describe the histology of the myocardium as follows. It is composed of a network of cytoplasm of varying thickness (2-4 mikrons). In those places where the muscle is cut tangentially, the muscle cells appear in the form of hollow cylinders surrounded by delicately striated protoplasmic walls. The nuclei of the interstitial cells are for the most part compressed. The muscle nuclei are peripherally situated. *Best's* carmin stain shows the intracellular non-protoplasmic areas to be filled with rods and droplets which stain a deep brilliant red.

Humphreys and *Kato*, in describing the results of the microscopic examination, stress the hypertrophy and vacuolisation of the heart muscle fibers. In their first case the largest fibers, up to 50 mikrons in diameter, were situated close to the endocardium and some of these probably were fibers of the *Purkinje* type.

As a result of the recognition of the fact that many cases of so-called idiopathic hypertrophy of the heart are due to an abnormal accumulation of glycogen, an old question comes to the fore. It concerns the relation between the so-called idiopathic hypertrophy of the heart and the rhabdomyomata of the heart. *Virchow* had supposed congenital hypertrophy of the heart to be caused by a diffuse formation of rhabdomyomata. And, indeed, it appeared that the greater part of the rhabdomyomata of the heart are built up by muscle cells rich in glycogen, and in some cases a transition between isolated and diffuse rhabdomyomata of the heart could be found (*Schmincke*). This question has been extensively discussed by *Pompe*, further by *Antopol* and co workers, and by *Humphreys* and *Kato*.

Pauli has recently described two cases of congenital diffuse rhabdomyomata of the heart in one family. The microscopical picture

of the heart muscle fibers, at least in one case, closely corresponded to that found in cases of glycogen heart. It stands to reason, therefore, that in reality one had to deal with two cases of glycogen heart occurring in one family.

The finding of glycogen infiltration in the heart, in a case of so-called idiopathic hypertrophy of that organ made *Pompe* raise for the first time the question to what extent this infiltration afforded a new and more general explanation of idiopathic hypertrophy of the heart. The fact that this infiltration could also be found in nearly all the other organs in this disease, suggested a general disturbance of the metabolism as the cause. The experience obtained since the publications of *Pompe* and *Putschar* has taught us that many cases of so-called idiopathic hypertrophy of the heart can indeed be explained in this way. *Pompe* himself in 1936 reported several cases observed in the Netherlands. Besides these cases, however, there occur in babies cases of idiopathic hypertrophy of the heart in which the accumulation of glycogen in the fibers of the heart muscle is lacking (see among others *Debré*, *Busson* and *Lhoste*, *Debré*, *Marie* and *Bernard*, *Mutgeert* and *Mansens*). For these latter cases provisionally the name idiopathic cardiac hypertrophy must be maintained.

In the literature up to 1932 *Pompe* could find only four cases which were in accord with his case as regards the histological appearance of the heart muscle. Two of these cases were of recent date (*Steiner* and *Bogin*, *Sprague*, *Bland* and *White*). Although the presence of glycogen had not been investigated in these four cases, he was of opinion that, because of the similarity of the histological appearance, he was justified in calling them cases of idiopathic hypertrophy of the heart due to glycogen accumulation. One of these four cases was "an enormous enlargement of the heart with vacuolisation of the muscle fibers, as well as vacuolisation of the hepatic cells," described by *Sprague*, *Bland* and *White* in 1931. — From a note in the article of *Humphreys* and *Kato* on page 599 it appears, indeed, that carmine stained granules were demonstrated in 1934 in the formalin fixed myocardial fibers by Dr *Tracy B. Mallory*, who had done the autopsy in the case of *Sprague*. On the same grounds case 4 of *Humphreys* and *Kato* was included in this group.

In a case recently described by *Ellis*, in a girl of four months, the

possible presence of a cardiomegalia glycogenica was "suspected too late after the autopsy which also was not carried out until 48 hours after death" The histological aspect of the heart muscle fibers with the peculiar vacuolisation was, however, typical and in this case also the *skeletal muscles* gave the same picture. *During life the latter felt rather increased in size and firm* It is not only possible, as the author writes, but in our opinion highly probable, that this was a case of glycogen disease, in which the muscular system was principally involved No particulars of the metabolism during life are given

We recall also that in two of the cases of *Humphreys* and *Kato* the skeletal muscles showed the same typical changes, and that in one of these cases the vacuoles contained much glycogen Increase in size of the skeletal muscles was not mentioned here

In the case recently reported by *Wolff* the tongue in addition to the heart showed an enormous accumulation of glycogen The latter had given rise to severe damage of the tongue muscle fibers Clinically severe functional disturbances related to the enlargement of the tongue were noted in this case and in the case reported by *Hertz* and *Jeckeln*

Is clinical recognition of idiopathic hypertrophy of the heart, caused by the accumulation of glycogen, possible? Though of late more of these cases have come to autopsy, still our knowledge with regard to the symptoms shown by the patients during life and with regard to their metabolism is greatly limited One is inclined to consider the possibility of the existence of a so-called idiopathic hypertrophy of the heart, when at examination a large heart is found without valvular lesions or an anomaly of development of which the enlargement may be the consequence But notwithstanding this, the diagnostic difficulties are manifold The hypertrophy of the heart due to glycogen accumulation is found as a rule in children who were normal at birth and who, until shortly before death, have not shown particular complaints

This was the case in the patient described by *Pompe*, for example This child was observed by us for some days before death The patient was a girl of seven months, who had fallen ill ten days previously and was soon in a critical condition The child had formerly

been in good condition her development after birth had been normal —The case described by *Antopol*, *Heilbrunn* and *Tuchman* was that of a boy of four and a half months who from birth had had an abnormal rapid respiration, but who until one month before admission into the hospital had shown a rather normal bodily development —In the cases described by *Humphreys* and *Kato* there were more complaints In their first case the clinical diagnosis was left sided lobar pneumonia and probably right sided bronchopneumonia, cardiac hypertrophy with mitral regurgitation, based on organic (congenital) defect A soft blowing *systolic murmur* had been heard at the apex and in the left midaxillary line —In their second case the clinical diagnosis was unexplained cardiac hypertrophy, possibly with endocarditis An inflammatory process had been ruled out by an X-ray film —Their fourth patient, a girl, was weak at birth At the age of seven weeks she had pneumonia Dyspnoea, high fever and increasing prostration preceded death at the age of six months The clinical diagnosis was idiopathic hypertrophy of the heart In other cases dyspnoea after effort and arrest or retardation of growth was noticed during some time before the infant became seriously ill Sometimes also edema or cyanosis were temporarily noticed in an earlier stage

That we have to do with a patient suffering from heart disease is obvious as a rule But it may happen that a so-called *splenopneumonia* of the left lung, especially of the lower lobe, or some other pathologic pulmonary condition, can give a clinical picture, which can only with difficulty be differentiated from the glycogen heart with pneumonia (or more properly from a pneumonia in a patient with general heart hypertrophy) In the child of *Pompe* one could not have thought of the possibility of an idiopathic hypertrophy of the heart due to glycogen accumulation, and here the diagnosis “splenopneumonia” was the most probable one —By Rontgenological examination we can as a rule recognise with certainty the existence of hypertrophy of the heart, however, whether this hypertrophy is an idiopathic one, and, when this holds true, whether it is founded on glycogen accumulation, cannot be determined by the X-ray Here we encounter the same difficulty that is usually found in many congenital heart defects, a certain diagnosis is made clinically and at the autopsy one is surprised by totally unexpected findings

The age of the patient is only of little value. Nearly all the certain cases of a glycogen heart were in children who died between the ages of four months and one year, and rather suddenly as a rule. As to idiopathic hypertrophy of the heart in general it is assumed that the patients reach the average age of one and a half years, the eldest patient was four years old. In nearly all the cases heart murmurs were lacking during life, but not constantly. Here we have the origin of many mistakes, the more so since it may occur that a cardiomegalia glycogenica is combined with a slight aortic stenosis (as we observed in one case).

The patient (a girl) recently described by *Hertz* and *Jeckeln* died at the age of forty days and clinically had given the impression of myxoedema. At the autopsy, however, no definite abnormality of the thyroid gland was found. The possibility that a more complicated endocrine disturbance (functional pituitary disturbance?) existed in this case, is discussed by *Hertz*.

Whether the electrocardiogram is of any help is doubtful. In the cases of congenital hypertrophy which cannot be classed as idiopathic in the strict sense, it may be of help. Here we are thinking more especially of the congenital hypertrophies incident to abnormalities in the heart muscle, such as interstitial myocarditis, whether or not caused by changes in the coronary vessels, cases which formerly were unjustly considered as belonging to the idiopathic cardiac hypertrophies (*Stoloff*, *Kugel* and *Stoloff*). These cases deserve special attention also from other points of view. Clinically the distinction from cases of glycogen heart is usually very difficult. Pathologically the findings may be most interesting. In 1924 *Carrington* and *Krumhaar* described a morbid picture in a girl of ten months under the title "so-called idiopathic cardiac hypertrophy in infancy." The patient died at the age of one year. The weight of the heart was 136 gm. The left coronary artery originated from the pulmonary artery and there was slight fibrosis of the myocardium. Microscopically there were found areas of very large vacuolised muscle fibers. Thirteen years later *Finkelstein* still was able to demonstrate the presence of glycogen in these fibers. Histologically the structure was different from that found in rhabdomyomatosis, but rather resembled that of the heart muscle fibers in the glycogen heart. To make a

distinction from the more diffuse abnormalities found in the glycogen heart *Finkelstein* introduced for such cases the name *cardiomegalia glycogenica circumscripta*. Before the article of *Finkelstein* had reached us, we observed with Dr *van der Linde* an analogous case of *cardiomegalia glycogenica circumscripta* in a girl of five months. During life the diagnosis of glycogen heart was considered probable. At the autopsy also in this case there existed a congenital malformation (very wide foramen ovale, combined with a wide pulmonary artery), which abnormalities must have caused circular disturbances—Histologically, in addition to areas of vacuolisation and glycogen accumulation which showed a striking correspondence to that of the heart in cases of *cardiomegalia glycogenica*, there were also regressive changes in the myocardium (increase of connective tissue, necrosis, fatty degeneration). The distribution of the glycogen field was principally but not exclusively subendocardial. Several explanations can be given to explain this circumscribed *cardiomegalia glycogenica*. In how far the condition is related to glycogen disease can only be established by a more thorough study with which we are now occupied.

That cases of hypertrophy of the heart due to glycogen accumulation should be recognized during life by a closer study of the metabolism is an expectation which thus far has not been fulfilled. This is partly due to the fact that the patients do not come to the doctor until rather late, when there already exists a complicating pneumonia, for example—The alterations in the metabolism, more or less typical for glycogen liver, were absent in a case of idiopathic hypertrophy of the heart with absence of glycogen accumulation in the liver as established at autopsy. This case was studied by *Mutgeert*. The patient described by *Hertz* and *Jeckeln* showed absence of a so-called initial insulin hyperglycemia, but did show a severe, long lasting adrenalin hyperglycemia. The fasting blood sugar was nearly normal. Rontgenologically an enlarged heart was found. As the morbid picture in this case was very complicated, no definite conclusions with reference to diagnosis could be drawn.

Humphreys and *Kato*, in the light of the finding of typical vacuolar degeneration of skeletal muscle in two cases, combined in one case with the demonstration of much glycogen, suggest that biopsy of skeletal muscles may be useful in the identification of doubtful cases

of glycogen disease This possibility could also be inferred from the findings of *Ellis* cited above —The child of *Putschar* showed peculiar collapses with disturbances of consciousness, which, according to *Beumer*, must in retrospect be regarded as hypoglycemic attacks However, in other cases, reported since, we cannot find anything of this kind in the anamnesis of the patients Typical changes in the blood or in the urine, which can be regarded as characteristic for the diagnosis of glycogen heart, have thus far not been found In one of the cases of *Humphreys* and *Kato* the absence of acetone and diacetic acid in the urine shortly before death is stressed Acetone was also absent from the urine in the case which we were able to examine This does not prove, however, that there is no tendency to ketonuria or ketonemia in cardiomegalia glycogenica —More intensive study of the glycogenolytic enzymes is lacking, and close observation and study are required

Special characteristics which would play a rôle in the recognition of hepatomegalia glycogenica have thus far not been established in the cases of cardiomegalia glycogenica Evidence of a familial character of the disease was present only in the case of *Sprague* and co-workers The familial character existed in the cases described as diffuse rhabdomyomata of the heart by *Pauli* (see earlier), and perhaps also in the case of glycogen heart, described by *Mutgeert* and *Mansens* The absence of acetone and acetic acid in the urine shortly before death is stressed in several cases Special adiposity, or the external symptoms of an endocrine disturbance, have rarely been observed Adrenals, thyroid, hypophysis and pancreas rarely showed alterations in the cases examined Pigmentation was lacking

Notwithstanding the very insufficient knowledge of the metabolism in the cases of cardiomegalia there are many arguments which speak in favor of accepting one cause in common for the cardiomegalic and for the hepatomegalic type of glycogen disease. In both types stress is laid on the extraordinarily large amount of glycogen accumulated in the organ concerned, and on the abnormal resistance of this glycogen to splitting, which under other circumstances may disappear In both types the accumulation of glycogen is, furthermore, not restricted to the organ that is clearly visibly enlarged What is the reason why at one time the cardiomegalic type appears, at another the hepato-

megalic? A definite answer to this question cannot be given at the present time. Much will depend on the results of an extensive investigation of the metabolism in children in whom the diagnosis cardiomegalia glycogenica was suspected during life and confirmed at autopsy.

The peculiar behavior of the cardiac glycogen, as compared with that of the skeletal muscle and the liver, (well-known from different observations), gives us only a partial indication. In the depancreatized animal, for example, the glycogen content of the muscles and of the liver diminishes, whereas the glycogen of the heart¹ does not diminish or may even increase. This might point to a rôle played by the islands of Langerhans. However, cardiomegalia glycogenica, as described above, is sometimes combined with hypertrophy of the skeletal muscles, caused by the accumulation of glycogen. Moreover, in cases of glycogen heart there is always present at the same time an accumulation of glycogen with the typical resistance in other organs which do not show hypertrophy. We might arrive at the conclusion that there exists a so-called pluriglandular disturbance, for the abnormal resistance of the glycogen of the skeletal muscle has been described in adrenal insufficiency, and that of the heart in pancreas insufficiency. Lesions of the pancreas or of the adrenals were rarely found in cardiomegalia glycogenica. This is only a minor argument against the rôle of these organs, as there is a great contradiction between pathologic findings and functional disturbances in organs with internal secretion.

In the light of recent investigations it is possible that in glycogen disease also a disturbed hypophyseal function will ultimately be assigned the etiological rôle, to explain the apparent pluriglandular disturbance (see chapter 6). But even if cardiomegalia glycogenica is related to definite endocrine factors, in addition those local factors will have to be considered which, during fetal life, influence the accumulation of glycogen on the ground that under certain circumstances they may retain their function after birth.

4 GLYCOGEN ACCUMULATION ACCOMPANIED BY HYPERTROPHY OF ORGANS OTHER THAN LIVER AND HEART

The more general significance of abnormal glycogen accumulation in the hypertrophies of organs was first evident from the fact that

the children described in 1929 by *von Gierke* showed in addition to the hypertrophy of the liver an *hypertrophy of the kidneys* with an enormous accumulation of glycogen. Here, also, *von Gierke* sought a relationship to the glycogen accumulation found in the embryonic kidney. In addition to these in the few cases of glycogen liver which have come to autopsy (the findings in cases where hypertrophy of the heart predominated were discussed separately), the combination of hypertrophy of liver and kidneys, caused by glycogen accumulation, was rarely found. Recently *von Gierke* himself described a case of glycogen liver in which an enlargement of the kidneys was absent. Such an hepatonephromegalia glycogenica was present in the case described by *Faber* (with 5.9 per cent glycogen for wet weight of kidney) and in two cases described by *Krakower*. In the first case of *Krakower* the kidneys in spite of being kept for several months in fixation fluid contained 11.5 per cent of glycogen in terms of dry weight. (According to *Popper* and *Wozasek* the kidneys ordinarily contain 0.29 to 0.69 per cent of glycogen, rising to 0.97 and 1.64 per cent in diabetes.)

In the numerous cases of glycogen liver which have been examined more or less extensively by clinical methods only, the simultaneous existence of a nephromegalia has been mentioned only once. *Wildcr* in his case made the diagnosis of hepatonephromegalia because in addition to a greatly enlarged liver there could be seen in the X-ray the shadow of an enlarged kidney. The recognition of a nephromegalia glycogenica will certainly not be a simple matter. *Lindsay* and his co-workers tried to demonstrate the existence of large kidneys by intravenous injections of uroselectan, but on account of the very large liver the outline of the kidneys could not be well recognized. The possibility of deducing the existence of a glycogen accumulation in the kidneys by the occurrence of a great deal of glycogen in the urine is very slight, as mentioned before, regardless of whether those kidneys are enlarged or not. One investigator examined the urine of a patient with glycogen liver for the occurrence of glycogen, but found nothing. It must be noted, however, that the method given for this examination, which was proposed by *Capppenberg*, must now be considered as being totally unsuitable.

However, to understand the differences in metabolism in glycogen disease, it is important to know whether much glycogen is accumulated in the kidneys, the more so when this accumulation is accompanied by

a marked enlargement of these organs We allude here, in the first place, to the increased excretion of diastase in the urine found in many cases of glycogen liver, which had been related by some authors to a changed permeability of the kidney (caused by the accumulation of glycogen?) Furthermore, it is very probable, in view of the significance of the kidney in the destruction of ketone bodies, that the metabolism of these ketone bodies will be altered when an accumulation of glycogen is present in the kidneys Adequate investigations which would have great importance, also, in the diagnosis of this condition, are still lacking, however

Experience has taught us that the possible rôle of glycogen in hypertrophies of other organs will be of great interest

Congenital *hypertrophy of the pylorus* appears in the minority of the cases (in our own experience) to be related to a marked accumulation of glycogen in the musculature of the pylorus In examining at autopsy the pylorus muscle of a baby, who gave the typical clinical picture of congenital hypertrophy of the pylorus, the smooth muscle fibers showed a picture greatly resembling that found in idiopathic hypertrophy of the heart caused by accumulation of glycogen All the vacuoles present in the muscle fibers appeared to be overfilled with glycogen Prof *Deelman* also found an analogous overfilling of the muscle fibers of the pylorus with glycogen in a case of very large clearly circumscribed hypertrophy of the pylorus in a woman of thirty-one years, who had suffered from stomach ailments during her entire life In recent years we have several times been able in cases of congenital hypertrophy of the pylorus, thanks to the cooperation of some colleagues, to examine the pylorus or some muscle fibers of the pylorus removed at a Rammstadt operation for the accumulation of glycogen in the muscle cells In these cases the result has always been negative

Of interest is the accumulation of glycogen which has been discovered by some authors in *voluntary muscles*, either by quantitative determination, or microchemically This glycogen accumulation has been found in cases in which hypertrophy of the liver predominated, as well as in those in which hypertrophy of the heart predominated, and in both groups the glycogen in the muscles showed the same properties Much glycogen has been found in the voluntary muscles in

our case of cardiomegalia glycogenica. In those cases which were examined histologically a typical degeneration with vacuoles was found in the striated muscle fibers. In some of these cases glycogen could be demonstrated in the vacuoles.

These findings direct attention to the possibility that some cases of *muscle hypertrophy* might belong in the syndrome of glycogen disease. Indeed *Ellis* found in a recent, almost certain case of glycogen heart that during life the muscles on palpation seemed "rather increased in size and shape." Experimental and extensive clinical research will perhaps offer the possibility of differentiating these from other forms of hypertrophy of the muscles. The fact that in some cases of this disease the striated muscle fibers showed the typical changes in their structure may be of significance for the diagnosis of glycogen disease *in vivo* (see *Humphreys* and *Kato* in the chapter on the glycogen heart). However, the presence of glycogen is not a constant finding (*Faber, Schall, von Gierke*).

In addition to these findings we have at our disposal observations on the accumulation of glycogen in other organs, among which the *central nervous system* should be particularly mentioned. (*Unshelm-Kimmelstiel* in a case of glycogen liver found glycogen in different areas of the brain, especially in the medulla, *van Creveld* by the use of quantitative methods in a case of glycogen heart found much glycogen in the spinal medulla). Here, there is also the possibility that a relationship exists between clinical symptoms referable to the central nervous system, and the special localized accumulations of glycogen in the brain (convulsions, epilepsy, idiocy).—This question is of special significance for the explanation of obesity of varying types, as found in many cases of glycogen liver. Is this obesity always primarily of an endocrine nature, or is it connected with disturbances in the *regio hypothalamica*, caused by the accumulation of glycogen? Clinically there is, on the one hand, resemblance to the obesity in dystrophia adiposo-genitalis, where the neurological cause is known, on the other hand, there often is resemblance to the distribution of fat in *Cushing's* syndrome, which is of endocrine nature (*Barr*).

That much glycogen may be found in parts of the central nervous system is a fact which has been much studied from both the phylogenetic and the ontogenetic points of view. The finding that glycogen

in glycogen disease may also accumulate in these places in itself speaks in favor of the view, which we also share, that in this disease one is justified in speaking of the continuation of a fetal condition

Whether there exists a form of glycogen disease in which the chief accumulation of glycogen is in the brain (or in the spinal medulla) is still an unsolved problem. If it occurs, then to a certain degree there should exist an analogy with amaurotic idiocy, the disease of *Tay-Sachs*. One becomes convinced more and more that in this disease we have to deal with a general metabolic disturbance, closely related to the disease of *Niemann-Pick* where, however, the localisation is preponderantly, although not exclusively, in the cerebrum. *Von Gierke* reckoned glycogen disease with thesaurismoses, to which also the lipoidoses belong.

5 DIFFERENTIAL DIAGNOSIS

Are the symptoms of hepatomegalia glycogenica, as found in both our patients and described in many other cases since published, characteristic for this disease? The question has great importance for the differential diagnosis of glycogen liver from other chronic liver diseases which give rise to enlargement, and in separating enlargements of other organs due to accumulation of glycogen from enlargements caused by other conditions such as tumors (e g, adrenal tumors and kidney tumors). The question is also of importance when a decision must be made concerning the advisability of laparotomy in a doubtful case. In our first patient, before he came under our care, a laparotomy was done because of the possibility of a neuroblastoma with metastases to the liver (type *Pepper*), giving rise to marked enlargement of that organ. Our own experience and the experience of others, as recorded in the many recent publications on glycogen disease with marked hypertrophy of the liver, permits an affirmative answer to the above question in the great majority of cases of glycogen disease. In hepatomegalia glycogenica there exists a series of clinical and biochemical symptoms, varying greatly in different cases, which have never been observed in other chronic liver affections, at least not in this combination.—The abdomen is very large, the enlargement being due to great increase in size of the liver. The history indicates that the enlargement of the liver was present at birth or appeared soon

afterwards. It is painless, for a time the increase in size is progressive. The surface of the enlarged liver nearly always is smooth. The general condition of the patient, even after the enlargement has existed for many years, remains good for the most part. Eventually other organs become hypertrophied but not the spleen—or the spleen becomes only slightly increased in size— In the greater number of the cases described chronic hypoglycemia in the fasting condition combined with ketonuria is present. When as sometimes happened in one of our patients, no ketonuria was present in the fasting state, the existence of a ketonemia could still be demonstrated. After the injection of adrenalin, usually, there is an absence of a rise or only a slight rise of the blood sugar, whereas the adrenalin effect in other respects is abnormal also. Next among the other abnormal effects are the slow disappearance of the ketonuria, which in the earliest stage not rarely increases, and the abnormal blood sugar curve, these abnormal effects develop after giving different carbohydrates, almost always without any marked excretion of sugar in the urine. No distinct deviations from the normal in the morphological or physical properties of the blood are observed. Increased blood glycogen and blood lipoids, particularly an increase of the cholesterol have been observed. Often there is a peculiarly localized adiposity, and the aspect resembles that of patients with an endocrine disturbance.

On the other hand, in hepatomegalia glycogenica, in so far as the cases have been investigated, clinical symptoms and laboratory findings which are present usually in an earlier or later stage in other kinds of chronic liver enlargement (especially cirrhosis of different origins) are absent for the most part. We refer to chronic jaundice, edema, ascites, severe haemorrhages, enlargement of the spleen, urobilinuria and a positive galactose or fructose test or both. Further, other features, often present when the enlargement is accompanied by destructive processes, are lacking, such as a very marked increase of the globulin content of the blood serum, a highly positive Takata-Ara reaction (the result is usually parallel to the increase of the globulin content), a marked decrease in the quantity of cholesterol esters in the serum and abnormal results of various other liver function tests.

There are in the literature several reports of children with enlarge-

ment of the liver, mostly cirrheses, with anomalies in the carbohydrate metabolism more or less similar to those found in the majority of cases of glycogen liver. In these cases there often existed along with a (hepatogenic) hypoglycemia of varying degree in the fasting condition, a tendency toward the appearance of hyperglycemia and excretion of sugar in the urine after the ingestion of sugar. This was especially the case after the ingestion of fructose and galactose, the sugars which are used in the examination of the glycogenetic function of the liver. Clinically and pathologically, the symptoms of a cirrhosis were found in these cases for the most part (*Knauer* and *Friedlander*, *Warkany*, *Halbertsma* and others). Among these cases only the patient of *Warkany* showed ketosis in the fasting state. The reaction after the ingestion of carbohydrates pointed to the fact that the glycogen content of the liver was small. This was confirmed by such autopsy observations as were made, particularly in the autopsy performed by *Hamperl* in the case of *Warkany*. In some cases, then, the analogy with glycogen liver was clinically striking and the analogy held in respect to the disturbance in carbohydrate metabolism. How complete a correspondence existed cannot be stated as a more detailed investigation of the metabolism was lacking (*Theones*) and clinically there were some differences.

More recent investigations in which the metabolism was studied more extensively, have taught us that the differential diagnostic difficulties between glycogen liver and liver cirrhosis sometimes indeed may be large, though the differentiation is not impossible. According to our own experience this possibility exists especially when the liver cirrhosis has not been present so long that all the typical clinical symptoms have developed. In this way we think we are able to explain at least one of the cases reported in 1936 by *Harnapp*.

Harnapp described two cases of liver cirrhosis, in which the diagnosis was proved by biopsy, though in the second case the possibility of a malformation of the liver could not be excluded. Nearly all the symptoms typical of liver cirrhosis (such as enlarged spleen, ascites, jaundice, excretion of urobilin), were absent. In the first case hypoglycemia and acetoneuria were constantly present while the patient was fasting, whereas a tolerance test with fat gave a normal rise of the plasma fat (in liver cirrhosis a distinct rise would not occur). In the second case the only deviation

found in the metabolism was a slight increase of the cholesterol in the blood. The carbohydrate metabolism was quite normal in this case. The author concludes that glycogen liver and liver cirrhosis clinically may give rise to such analogous morbid pictures that a differential diagnosis is impossible. We are of the opinion that the author's observations do not justify this conclusion. As regards his first case we wish to remark that the response of the blood sugar to the injection of adrenalin was normal, that the tolerance test after fructose shows a slightly decreased tolerance and that the globulin content of the serum in consideration of the age of the patient (one and one-half years) was markedly increased (24.8 mgm %). This last fact, the author states incorrectly, according to *Bendien* and *Snapper* is a constant finding in parenchymatous liver affections. The author himself remarks further that clinically there were some symptoms in this case which were also unusual for glycogen liver—In his second case (a girl of seven years) retardation of growth was absent, the enlargement of the liver moderate, and the reaction to adrenalin normal—In both cases in our opinion there were thus sufficient grounds to make the diagnosis of liver cirrhosis instead of glycogen liver, especially in the first case.

The alimentary lipemia up to some years ago was thought to be absent in most cases of liver disease, particularly in cirrhosis. This made *Beumer* and *Loeschke* think that the presence of a persistent lipemia in their case of glycogen liver, after a meal rich in fat, was of diagnostic value. However, as mentioned before, recent investigations have greatly diminished the value of this test in differential diagnosis.

Changes in the nitrogen metabolism are often present even in the first phase of cirrhosis of the liver. It is, therefore, of importance that *Hertz* and *Biedermann* did not find changes in the nitrogen metabolism in their cases. *Hertz*, in this regard, points to the presence of such changes in the case of *Parnas* and *Wagner*, which also showed peculiarities in this respect.

Certain symptoms of patients with glycogen liver certainly cannot be regarded as being typical of that condition, still others may or may not be. Urobilinuria was constantly absent in the case of our boy, but not in that of our girl. The physical infantilism which is usually present when the disease exists for a long time very probably is not a typical symptom. This retardation of growth among other symptoms has been found also in the cases of congenital hypertrophy of the liver.

due to new growths, observed by *Υλppò*, and also is present in other parenchymatous liver diseases. As we pointed out previously, the underlying cause of this disturbance in growth in patients with glycogen liver may be quite different from that existing in patients with chronic parenchymatous liver disease. It is important to note, furthermore, that within a rather short time marked increase in length and in the development of the skeleton took place in several cases, including both our patients as well (see table at the end of this article).—The familial character of glycogen liver, found by some investigators, should not be regarded as being a typical circumstance since it is not so rare in cirrhosis of the liver. The same may hold true for the consanguinity of the parents which was found in a few cases (*van Creveld, Unshelm*)

From the series of cases of hepatomegalia glycogenica which have been described as such in recent years it has become obvious, as might be expected in view of the well-known dissociation of disturbances in liver function, that the intensity of some symptoms and the abnormalities in metabolism may vary greatly. However, as mentioned before, the possibility exists that the variations were in part caused by a difference in glycogen accumulation in organs other than the liver, especially in the muscles and the kidneys, or by a different pathological picture. But we think we are justified in rejecting the supposition that there may occur cases of glycogen liver (proved by biopsy or autopsy), in which all the metabolic deviations mentioned above are absent. Even the case of the infant of four months old, described by *Harnapp*, in which patient all metabolic symptoms were said to have been absent, in our opinion showed a resistance after the injection of adrenalin, as can be seen from the reproduced curve. Moreover, the anatomic diagnosis in this case was not irrefutable. At any rate it is of great significance that nearly all patients with glycogen liver in which the diagnosis was confirmed by biopsy or autopsy, as far as they had been examined during life, had shown a complex of symptoms resembling nearly wholly that of both of our patients. It may be possible that with the increasing age some of the symptoms disappear (see the chapter on the clinical course)

Pathologically, the picture in cases of glycogen liver is not always the same, this holds true, for instance, for the amount of fat or con-

nective tissue found in the liver, which is overfilled with glycogen. In our boy the appearance of the liver, as found at the laparotomy and his general adiposity indicate that his liver contained much fat, just as was found at autopsy in the first case of *von Gierke* and in the cases recently described by *Krakower*. In the first case of *Krakower* the fat content of the liver was even 52.3% of the dry weight. The possible significance from the standpoint of differential diagnosis of the ketosis and some other symptoms in these last mentioned cases of congenital steatosis of the liver, was stressed elsewhere in this article.—In our girl the constant urobilinuria and weak positive Takata-Ara-reaction indicate, perhaps, that in her case the connective tissue element is more increased, as was found in the second case of *von Gierke*. An increase of connective tissue in connection with glycogen disease indeed has been noted by other investigators (see *Lindsay* and co-workers) and this could explain the presence, in a few cases, of some clinical and clinical-chemical symptoms formerly regarded as typical of cirrhosis of the liver (*Exchaquet*). *Lindsay* and co-workers, on the basis of another case, even conclude that glycogen disease tends to produce cirrhotic changes in the liver. Provisionally we must say that experience does not agree with this conclusion.

The differential diagnosis between hepatomegalia glycogenica and congenital fatty liver ("stéatose hépatique massive" of *Debré* and co-workers) depends upon further clinical and metabolic study, as was discussed previously. The "stéatose hépatique massive" of *Debré* is a morbid picture characterized by a very marked painless hypertrophy of the liver, beginning at a very early age, and in which biopsy indicates the existence only of a very large accumulation of fat in the liver, it may show clinically not only an important difference from, but also a very marked resemblance to, the picture of the glycogen liver. It has been described by different authors and was observed as a familial affection by *Björum* who also gives the findings at autopsy. A detailed report of a case studied during life and at autopsy, was given recently by *Kramer* and co-workers. Some points which are of value for the differential diagnosis between hepatomegalia glycogenica and "stéatose hépatique massive" were discussed earlier in this article, and we indicated some points which might be of value in any further study designed to separate these two conditions.

Cases belonging to the so-called *reticulo-endotheliosis* group sometimes have to be differentiated from cases of glycogen liver, for in recent years it has become obvious that the proliferation of the reticulo-endothelial system which is characteristic of this group of diseases, may show great variety in localisation as well as in intensity. Among the so-called infective reticulo-endothelioses as well as among the group of cases in which the proliferated cells have accumulated substances which can easily be recognised (lipoidoses), there are cases in which the enlargement of the liver is prominent, and in which the symptoms manifest themselves in very young patients (*van Creveld* and *ter Poorten*). However, the differential diagnosis from glycogen liver, even in these cases, will not offer great difficulty. The aspect of the patient, the history and the course of the disease usually will be quite different. Moreover, even in these cases of reticulo-endotheliosis there will generally be a palpable spleen or typical localisation in the skeleton or the skin. Sooner or later the localisation in the liver will give rise to symptoms which are quite different from those in glycogen liver (haemorrhages, ascites, etc.). A study of the metabolism will show that the typical disturbances in carbohydrate metabolism found in glycogen liver are absent and that, as the disease progresses, deviations from the normal in blood and in liver functions will appear which resemble those in advanced cases of liver cirrhosis. A puncture of spleen or bone marrow to demonstrate the typical cells will hardly be necessary for the differential diagnosis from glycogen liver. The fact that familial cases occur both in the lipoidoses and glycogen liver (thus far less frequently in glycogen liver than in the lipoidoses) is of minor importance. As regards the race of the patients, many patients suffering from *Gaucher's* disease and, especially, those having *Niemann-Pick's* disease belong to the Jewish race. In only one case of glycogen disease described thus far was it noted that the patient belonged to the Jewish race (*Krakower*) and the father of our second patient (the girl) was a Jew too.

A morbid picture which must be distinguished from cases of glycogen liver, though in some respects it may be closely related to it, is the following. *Mauriac* described a *syndrome occurring in diabetic children* several months or years after insulin treatment had been started, a syndrome which is characterized by a progressive hepatomegaly with the development of a collateral circulation but without

splenomegaly, with arrest or retardation of growth and the development of a form of adiposity as occurs in adiposogenital dystrophy and in which the face becomes rounded like a full moon *Mauriac* believes that a close relation exists between this syndrome and the similar one occurring at an earlier age in glycogen liver and also in congenital hypertrophic steatosis of the liver. Analogous cases of hepatomegaly, occurring in children treated with insulin and which clinically may resemble very much the cases of glycogen liver but which by the anamneses may be distinguished from them, have since been observed, among others by *Mouriquand* and *Charleux*, *Aubertin*, *Nobécourt* and *Gjuric*. In the cases observed by *Aubertin* and in one of the two cases observed by *Gjuric*, the enlargement of the liver disappeared. *Gjuric* is of opinion that we have to deal here with the transition from diabetes into glycogen disease.

In this connection an observation of *Dupérit* and *Maupetit* deserves special attention. A boy of seven years died after an acidotic coma, accompanied by acetonuria and glycosuria. The boy had never been considered to be diabetic. He was observed in the hospital for two days only prior to his death. It appeared that the liver was palpable three finger breadths below the costal margin, thus in comparison with cases of glycogen liver the liver in this instance was only moderately enlarged. Treatment with large quantities of insulin and sugar caused the coma to disappear, but soon it returned. A blood sugar determination could not be made.—At the autopsy marked retardation of growth was noted. The subcutaneous layer of fat was minimal. The weight of the liver was 1031 gm (normal value for the age no more than 650–700 gm). The heart was relatively large. Notwithstanding the fact that pieces of the liver have been kept for more than two years in 10% formalin and that this formalin has been replaced by a fresh solution repeatedly, these pieces still showed glycogen in many liver cells. On microscopic examination the cells were conspicuous by their large size, they were pale and filled with vacuoles. In addition a slight fat formation in the rest of the liver cells was present and slight evidence of cirrhosis. In the pancreas the islets of Langerhans were not numerous, but were apparently normal in appearance. Cells of the heart muscle were normal. The kidneys showed no abnormality, glycogen staining is not mentioned.

The authors consider it highly improbable that this was an ordinary

case of diabetes mellitus with a terminal coma. They attach special significance to the enlarged liver and to the finding of glycogen in so many liver cells. They consider their case to belong in the category of glycogen disease and that it would represent a form of this disease with a serious prognosis and glycosuria. They suggest three possibilities to explain the seriousness of this form: an insufficiency of the internal secretion of the pancreas in addition to some other metabolic disturbance of unknown nature, an alteration in the stability of the glycogen which might permit a glycosuria through a sudden overfilling of the circulation with glucose, and a diabetes of hepatic origin.

Though the observations are not complete and the case is somewhat different from the cases of *Mauriac* and others just mentioned (moderate enlargement of the liver and no abnormal accumulation of fat), it draws our attention to an aspect of the problem which may have a special significance, namely the possibility of the transition of diabetes mellitus, under certain conditions, into glycogen liver.

There are other points which suggest a *relationship between glycogen disease and diabetes mellitus*. In families of children with a glycogen liver there occurred some cases of diabetes mellitus (a.o. *Sundal*, *Ellis* and *Payne*, *Harnapp*). The much discussed morbid picture of *Parnas* and *Wagner*, which showed great resemblance to glycogen liver, gradually developed into a case of diabetes mellitus. As to the metabolic changes in glycogen liver we must further point to the blood sugar curve which usually shows much resemblance to that found in diabetes except for the hypoglycemic point of departure. Secondly we may point to the lipemia and to the ketosis which frequently occur in both diseases and for the most part have an analogous origin, namely, the insufficient combustion of carbohydrates in the metabolic mixture. In glycogen liver this is caused by a shortness of available carbohydrates because not enough glycogen is broken down, in diabetes mellitus there is an intensified glycogenolysis but an insufficient combustion of sugar. — From a pathological point of view little correspondence has as yet been found between the diseases, the principal being the partition of fat in different organs (*Krakower*) and the accumulation of glycogen in the kidneys. The discussion of the pathogenesis of glycogen disease will give us once more the occasion to refer again to a possible relation with diabetes mellitus.

6 PATHOGENESIS

The cause of the difficulty in splitting the glycogen in glycogen disease is not yet definitely settled. As previously mentioned, the blood in the cases of glycogen liver showed a normal, sometimes a sub-normal, diastatic activity. It was originally thought by *Schönheimer* and *von Gierke*, that diastase was absent from the liver or diminished. This should cause the accumulation of the glycogen *in vivo* and explain the disturbance in post mortem splitting of glycogen which was first encountered in the liver. Afterwards it was found by other investigators in other organs, also. However, as already stated, this conception had to be rejected because of the fact that in cases of glycogen liver an excess of diastase was found in the liver (*Unshelm*). Further, it appeared that the liver-glycogen in cases of glycogen liver and the heart-glycogen in cases of glycogen heart could be converted by the action of normal liver and normal heart respectively. Thus glycogen and glycogen splitting ferment were both present but could not act. How is the glycogen protected in so particular a fashion in this disease? *Lesser's* theory was that a modification in the colloidal state of the liver cell was necessary for the liberation of glycogen. An alteration in the colloidal state of the cell could disturb the glycogenolysis and thus contribute to the accumulation of glycogen. Does the glycogen in glycogen disease form a compound with protein or have we to deal here with some other modification of glycogen, or are the local conditions for the ferment-action unfavorable, or is there lacking a factor which normally interacts between glycogen and glycogen splitting ferment? All these possibilities have been considered in recent years.

The conception of a glycogen difficult to split owing to an abnormal binding with protein (a conception mentioned by *Unshelm*), has been investigated by us with the help of Dr *W. M. Bendien*, in ultrafiltration experiments with the blood serum of our patients and that of some control children. No evidence for the existence of such a particular combination of the glycogen could be obtained thus far by this method of study. However, the difficulty in splitting the blood glycogen in both of our patients might be interpreted as indicating the existence of an abnormally bound glycogen. From ferment studies with liver tissue in a case of glycogen heart *Hertz* concludes that an abnormal binding of glycogen with protein (*Unshelm*) is probably not the cause.

of the difficult splitting of glycogen in glycogen disease—But the evidence for the existence of complex compounds of glycogen and proteins has increased in recent years. The experiments of *Willstätter* and *Rohdewald*, mentioned above, have opened a new field of investigation in this direction. The same holds true for the experiments recently published by *Myskowski* and performed in *Svedberg* Institute. In these experiments the binding of glycogen to serum and serum proteins was studied by means of the ultracentrifuge.

Kimmelstiel thought that the chemical constitution of glycogen in glycogen disease might be different from that of normal glycogen. This abnormal glycogen might be split only with difficulty and might be formed by the polymerisation of a heterotype form of blood sugar. *Faber* and *Vendég*, however, were unable to confirm this explanation.

The conception that in glycogen disease there is lacking a factor which normally interacts between the glycogen and the glycogen-splitting ferment becomes more and more probable. Recent investigations have revealed the existence of new influences playing a rôle here. In the first place, there exists a nervous influence on liver glycogen which can express itself otherwise than through adrenalin and insulin. On the basis of these findings *MacLeod* even speculated as to the existence of two forms of glycogen in the liver, having a different functional behavior. Clinically, diseases of the diencephalon (hypothalamus) especially may give rise to disturbances in the carbohydrate metabolism. Furthermore, we must point to the results of recent important investigations on the influence of hormones, especially of the anterior lobe of the pituitary and perhaps also of the adrenal cortex, upon carbohydrate metabolism, and also possibly to the properties of glycogen in different organs.

Viale, who considered the adrenal as a regulator of the carbohydrate metabolism, found that following the extirpation of the adrenals the muscle glycogen did not disappear after death, or it disappeared only slowly—even after incubation at 37°C for several hours. Thus this glycogen showed a property which we find in glycogen disease.

The fact that (according to the classic investigations of *Houssay* and his co-workers, and of many others,) pancreatic diabetes in cold and warm blooded animals is greatly relieved by hypophysectomy, especially by the removal of the anterior lobe, also indicates an in-

fluence of the anterior lobe of the hypophysis on glycogenolysis (*Iucke*) Removal of the anterior lobe of the hypophysis causes glycogenolysis to take place with much greater difficulty (*Corkhill, Marks and White*) Under these circumstances adrenalin is less effective in causing a rise of blood sugar, eventually causing glycosuria, and the sensitivity to insulin is highly increased (for literature see *Collip*, 1935)

Perfusion experiments with the liver of operated and non-operated animals, which have the advantage that the influence of other glands of internal secretion are eliminated, also seem to have proved that the anterior lobe of the pituitary exerts an influence on glycogenolysis (*Fluch, Greiner and Loewi*)

The pancreotropic hormone of the pituitary, described by *Anselmino* and *Hoffmann*, should decrease the glycogen content of the liver Such an effect would be produced especially by a "carbohydrate metabolism hormone" which *Anselmino* and *Hoffmann* consider they have isolated from the anterior pituitary lobe This hormone was demonstrated in the blood of normal men after giving carbohydrates, and in the blood of fasting diabetics The possibility is suggested that glycogen disease is related to the absence of this hormone This supposition could, however, not be confirmed by *Hertz*, who investigated the blood of two patients for the presence of this "carbohydrate metabolism hormone"

The possibility that a disturbance in pituitary function may be the cause of the peculiar stability of glycogen encountered in glycogen disease finds a support in the recent experiments of *Thompson and Cushing* These authors wished to produce experimentally the morbid picture of a basophile adenoma of the hypophysis A series of injections of active gonadotropic hormones into young animals brought about retardation in growth and adiposity among other things, along with this the liver was slightly enlarged and the histological picture of the liver and of the muscles resembled that seen in glycogen disease

As regards the special character of the glycogen in the heart muscle, attention must be drawn to the effect of removal of the pancreas on the glycogen content of heart, muscles and liver It appeared that, whereas muscle glycogen and especially liver glycogen were diminished

greatly, there was no decrease in the glycogen content of the heart muscle. Not rarely an increase even was noted (*Best*). In every case the heart glycogen showed an increased stability.

Furthermore, the experiments on the effect of the so-called ketogenic hormone of the anterior pituitary on liver glycogen must be mentioned at this point. A very important increase in the glycogen content of the liver was found by some authors after administration of this hormone, when given together with the thyroid hormone, the latter was unable to deplete the glycogen content of the liver (*Magistris, Chianca*).

Thus the recent investigations on the function of the organs of internal secretion have revealed the existence of some new factors of hormonal nature, which may be of the greatest importance in explaining the stability of the glycogen encountered in glycogen disease.

If we accept a hormonal cause for the accumulation of glycogen which can be mobilized with difficulty, two questions arise. *The first question* is how far this hormonal factor plays a rôle in an early period of life. From many experimental observations we know that glycogen occurring in embryonic life and also shortly after birth behaves functionally in a way differing from that in adults, but similar to that in glycogen disease. We have already put forward the hypothesis, on the basis of an extensive examination of premature children, that in our first patient there might have been the persistence of a fetal condition. It has to be accepted that the factors which during fetal growth influence the local accumulation and the fermentative breakdown of glycogen in organs, under certain circumstances keep their function in later life, and in this way cause a marked hypertrophy of one or more organs by the accumulation of glycogen. *Von Gierke* also thought of the possibility that in glycogen disease we may have to deal with the continuation of fetal conditions.

As regards the accumulation of glycogen in the fetal liver, the experiments of *Aron* must be mentioned especially. In these experiments the significance of hormonal factors for the accumulation of this stable glycogen was stressed. *Wertheimer's* experiments are also of significance, since they showed that in the fetuses of rats and guinea pigs the splitting of glycogen takes place only with difficulty, and that during the first days of life the glycogen can only with difficulty be mobilized by adrenalin. *Hertz's* orientating experiments on this phase

of the problem, mentioned before, show the measures which have to be taken before one is justified in drawing conclusions as to the stability of fetal glycogen

The second question is how far our present clinical and pathological experience in cases of glycogen disease now gives us the right to accept a hormonal cause for this condition, and which organ of internal secretion is particularly involved. The general opinion on this phase of the problem has become more settled of late as the result of study of many cases and of the several forms in which glycogen disease occurs and also as the outcome of the enormous development of knowledge which has taken place in recent years in the field of internal secretion.

In regard to the pathological findings in the proved or partially proved cases of glycogen disease it may be said that in general the changes found were slight ones and the possibility that they may have been related to diseases or infections preceding death cannot be excluded. In the first case of *von Gierke* the adrenals were slightly atrophied. In the case of *Unshelm-Kimmelstiel* some of the islets of Langerhans were hypertrophied, in the case of *Faber* they were few in number compared with the normal, and some were smaller while others were distinctly hypertrophied. Alterations of the cells of the Langerhans islets were also found in one of the cases described by *Krakower*.

The clinical findings have often been referred to as a dysfunction of the organs of internal secretion. The patient described by *Bellingham Smith* and *O'Flynn* showed marked pigmentation and abnormal growth of hair, symptoms which up to some years ago were always thought to point to an abnormal adrenal function—Our first patient shows some clinical symptoms of a disturbance in the function of the hypophysis, and the combination of hypoglycemia, abnormal blood sugar curve, sensitivity to small amounts of insulin, markedly decreased epinephrin hyperglycemia, ketosis, retardation of growth and adiposity, which he showed already many years ago, nowadays is considered strongly suggestive of a hypophyseal disturbance.

On the basis of the combination of hypoglycemia in the fasting condition with only a slight elevation of blood sugar after the injection of adrenalin alone, the occurrence of a hypofunction of the adrenal was suggested in several cases of glycogen liver.

Priesel and *Wagner* offered the hypothesis that in the case of *Parnas*

and *Wagner* there had existed from the beginning a disturbed function of the internal secretion of the pancreas

Formerly we had excluded the possibility of a hyperinsulinism in our cases on different grounds (a) The so-called hypoglycemic symptoms were lacking (b) It seemed to us that sensitivity to small amounts of insulin could not be expected when a hyperinsulinism existed (c) Acetonuria was present

We must remark, however, that hypoglycemic symptoms (epileptiform seizures, fits) are mentioned in some cases and that the sensitivity to insulin, first noticed in our boy, was not definitely present in the case of *Rauh* and *Zelson*. Acetonuria was not a constant symptom, but it was present in some cases where hypoglycemic symptoms were also noticed. This combination does not occur in hyperinsulinism—With the exclusion of the possibility of a hyperinsulinism—the high glycogen content of the liver might speak in favor of this conception—the possibility is rejected that glycogen disease, and glycogen liver more especially, represents the contrary of diabetes mellitus

The possible relationship between the neuro-hypophyseal system and glycogen disease was stressed by several authors. In the opinion of *Anderson* and of *Hertz* symptoms of a disturbed neuro-hypophyseal function may have been present in many of the published cases of glycogen liver. *Hertz* has strongly defended the conception that his patient was a hypophyseal dwarf. His case of glycogen heart gave also a definite impression of an endocrine disturbance

Anderson stresses the possible rôle played by the anterior pituitary in explaining many clinical symptoms of glycogen disease. In both his patients, as in ours, *Aschheim-Zondek* tests upon the urine gave negative results. In our patient (the boy), also, the chlorine metabolism was normal

Hildebrand, who himself did not describe a case of glycogen disease, but compared a number of cases published by others, came to the conclusion that many of the symptoms observed point to a disturbed pituitary function

Wilder raised the question whether the hepatomegaly in his case might not result from a disturbed carbohydrate metabolism occurring as the result of the internal hydrocephalus which exerted pressure changes in the region of the hypothalamus and pituitary gland. In

the X-ray the sella turcica in his case was within normal limits, but depressed, along with the whole middle cranial fossa

Erben and *Kilster* found an abnormal configuration of the sella turcica

Thus there is a very limited number of cases in which more or less definite symptoms were found, either pathologically or clinically, which pointed to a disturbed function of some one organ of internal secretion. The hypophysis has been investigated thus far in only a few cases which have come to autopsy, but no alterations have been found (*Krakower*, *Hertz* and *Jeckeln*, *von Gierke*). However, this negative result cannot be regarded as of great significance for two reasons. In the first place, parallelism between pathological lesions of an organ of internal secretion and clinical indication of a disturbed function is often lacking. In this respect we have only to remember the pathological findings in diabetes. *Warren* showed that the lesions found in the pancreas of diabetic and non-diabetic patients could be exactly the same. Secondly, as regards the slight changes in the islets of Langerhans and especially those in the adrenal cortex which have been found in cases of glycogen disease that have come to autopsy, recent investigations have shown the possibility that they were secondary. The same possibility holds in regard to those symptoms, encountered in several cases, which pointed to a dysfunction of either the pancreas or the adrenals. They all could have been caused by a primary pituitary dysfunction.

For many of the symptoms observed in different cases of glycogen disease in general, and of glycogen liver in particular, a hypo activity of the anterior lobe of the hypophysis or of the tuber cinereum seems to offer an adequate explanation. For other symptoms a hyper activity must be postulated. A hypo-activity may give an explanation of the stability of glycogen in glycogen liver, as in animal experiments glycogenolysis was produced with more difficulty after removal of the anterior lobe of the hypophysis. Hypoactivity could also explain such symptoms as the tendency to hypoglycemia with or without attacks, hyper-sensitivity to small amounts of insulin, abnormal sugar tolerance curves, decreased epinephrine hyperglycemia, abnormal fat distribution and fat development, retardation of the development of the skeleton and teeth and osteoporosis. Many

recent animal experiments have taught us that several of the symptoms which are met with in cases of glycogen liver are also encountered after experimental hypophysectomy, and may be explained by the presence of accompanying tuber injuries, or by alterations affecting the nutritional condition of the tuber. Thus far this explanation does not meet with great difficulties.

However, in regard to such important symptoms as the glycogen content of liver and muscles and other organs, the removal of the hypophysis in experimental animals thus far has not given constant results. One circumstance under which the glycogen content of the liver was found to be greatly increased was after long continued administration of the ketogenic hormone of the pituitary (*Magistris, Chianca*). *Collip* is of the opinion that, if glycogen disease is associated with pituitary malformation, it most likely would be the result of an overproduction of the ketogenic principle. Such an overproduction might perhaps explain some other symptoms (ketosis especially, further lipemia, adiposity).

So we have to conclude that in glycogen disease there are existing at the same time symptoms of a hypo- and of a hyperfunction of the pituitary. The fact that several of the above mentioned symptoms present in cases of glycogen liver do also occur under conditions in which a disturbed pituitary function has been established (pregnancy, eclampsia), in itself also speaks in favor of a rôle of the pituitary in glycogen disease. However, we must remember that opinions concerning the ketogenic and other pituitary hormones are still divergent, that neither ketosis nor lipemia is a constant symptom in glycogen disease and that in one of our patients during a period when ketosis was definitely present, no indication of the presence of a ketogenic hormone in blood and urine could be found (*Dingemans*).

If the hypertrophy of organs met with in glycogen disease is related to a disturbed pituitary function, then one is reminded of the opposite in hypophyseal cachexia (*Simmond's* disease), in which all the organs at autopsy are found to be small. Why, then, in glycogen disease, the hypertrophy is restricted to one or to some organs, is still obscure. The idea that the anti-hormones (*Collip*) present in all organs should play a rôle here, is thus far only a conjecture.

The final provisional conclusion must be that the modern physiology

of the endocrine organs, especially of the anterior pituitary, gives us an explanation of many symptoms of glycogen disease, especially of those occurring in glycogen liver. A general explanation of the morbid picture is lacking at the present time, however.

7 CLINICAL COURSE

In general, opinions agree in accepting the idea of a favorable prognosis for glycogen disease, more especially in cases of glycogen liver, in contrast to such diseases as neuroblastoma of the adrenal with liver metastases, and cirrhosis of the liver with or without a known etiology. With the exception of the patients in whom *von Gierke* and *Schönheimer* examined the organs after death, only a few cases have come to autopsy. In the first case of *von Gierke* the direct cause of the death was influenza, in the second case death followed pneumonia. The patient recently reported by *von Gierke* died from an otogenic meningitis. The patient reported by *Bellingham Smith* and *O'Flynn* suffered not only from a familial hepatomegaly but also from a chronic pulmonary fibrosis with bronchiectasies, and the authors write that "the patient whilst coughing was seized with violent abdominal pain and fatal collapse followed"—The child described by *Unshelm Kimmelstiel* died of a bronchopneumonia. The case of *Faber* is that of a baby born some weeks prematurely with a birth weight of 2400 gm, who died at the age of four weeks from a recurring dyspepsia. The child described by *Lindsay*, died from a bronchopneumonia, and also the patients, described by *Krakower*, died from respiratory infections.

The few cases which came to autopsy before 1929, and which in retrospect may be considered as being cases of hepatomegalia glycogenica, can be left out of account here. The cause of death in cardiomegalia glycogenica has been discussed elsewhere in this article.

Some authors are of the opinion that the patients with glycogen liver show a special sensitivity to infections. We cannot agree with them on account of the experience of other investigators and of our own. Both patients described by us, the elder of whom (boy) is now sixteen years old and the younger (girl) eleven years old, are in excellent condition. There neither have been nor are special indications of an increased sensitivity to infections. The particularly ex-

tensive observations on our boy showed that the disease may exist for years and years without giving rise to stormy symptoms

The study of both our patients revealed the following facts Length and weight increased in both children, the weight especially in the boy (see table), he thus gives the impression of corpulency It is important to state that at the age of twelve years all his teeth were still deciduous After that age he lost them The fasting blood sugar content in our boy during recent years has been increased The ketosis, which formerly was very marked, has nearly disappeared Other abnormalities in his metabolism are present as before The dimensions of his liver have slightly decreased There is still a

TABLE 1
Growth in glycogen disease
(Patients 1 and 2, van Creveld)

PATIENT 1, ♂			PATIENT 2 ♀		
Age	Length	Weight	Age	Length	Weight
<i>years</i>	<i>cm</i>	<i>kgm</i>	<i>years</i>	<i>cm</i>	<i>kgm</i>
10	132 0	36	6	100 5	19
12	143 5	45 5	7	104 5	19
13	147 0	48	8	111 5	22 1
14	151 0	51	9	117 5	22 9
15	154 5	51 5	10	123 5	25
16	156 0	55 1			

definite leucopenia After giving extra sugar the urine never contains any sugar

As for the girl, her maximal abdominal circumference has increased only slightly The bones of the wrist have developed to a great extent, and for the past years they have all been normally present (see tables 1 and 2) The dimensions of the liver are still about the same The abnormalities in the metabolism have also remained the same with the exception of a distinct rise of the blood sugar while in the fasting condition (in July, 1937, 0.083%)

In different articles in recent years, discussing the prognosis of children with glycogen liver, two patients are mentioned especially, that of *Parnas* and *Wagner*, and that of *Worster-Drought* As mentioned before, the liver in the patient of *Parnas* and *Wagner* has

become much smaller and the patient himself at the age of sixteen years became a subject of real diabetes mellitus. *Priesel* and *Wagner* are inclined to think that from the beginning there must have existed a disturbance in the internal secretion of the pancreas, an opinion founded on the course of the disease. Moreover, at the age of twenty years (in 1934), the patient was still markedly under-developed (personal communication to *Rauh* and *Zelson*).

Of those authors who are of the opinion that in glycogen liver we have to do with more than one type of change in metabolism, we mention specially the French investigators. In addition to a type

TABLE 2
Development of wrist skeleton in patient 2, ♀

AGE years	RIGHT WRIST	LEFT WRIST
5	Capitate + Hamate + Triangular +	Capitate + Hamate + Triangular +
5	Capitate + Hamate + Triangular + Multangular + (trace)	Capitate + Hamate + Triangular + Lunate +
7	The ulnar epiphysis and the navicular have not yet appeared on either hand *	
8	Wrist skeleton of both hands complete.	

* Normally in girls the navicular appears before the end of the fourth year and the ulnar epiphysis before the age of 6½ years.

characterized by symptoms such as we found in both our patients, and which should point to an insufficiency of the adrenals ("type *von Gierke van Creveld*," as they call it), other cases give a syndrome pointing to an insufficiency of the pancreas, with marked glycosuria and strong ketonuria (called "type *prédiabétique*" or "type *Parnas and Wagner*") This point of view is that of *Debré* and co workers, of *Dupérier* and *Maupetit*, and of others as well. The changes in the case of *Parnas and Wagner* on the one hand, and those in the case of *Debré* and co workers and *Dupérier* and *Maupetit*, on the other, when compared, show important differences. We mention only the inconstant glycosuria in the case of *Debré*, and the variations in the

blood sugar content after the injection of adrenalin In the case of *Dupérié* and *Maupetit*, to our great regret, there is no indication as to the state of the metabolism until very shortly before death

The case of *Worster-Drought*, according to the authors, indicates that the prognosis of glycogen liver may be excellent The first time that the enlargement of the liver was established by a physician was when the child was between two and four years old At the age of fifteen years the liver had become somewhat smaller, and at the age of twenty-two years it was no longer enlarged In 1935 the patient "still had occasionally acetone breath and traces of acetone in the urine" These last-mentioned symptoms indicate, however, that the metabolism was not yet quite normal A more extensive examination of the metabolism has not been carried out in this patient, and it still remains desirable to do so

In the case recently (1937) described by *von Gierke* of glycogen liver in a girl who reached the age of nearly fifteen years, the weight of the liver was still 2750 gm, which is at least $2\frac{1}{2}$ times the weight normal for this age It is unknown whether metabolic changes had occurred as the child grew older At death the habitus of the girl was infantile In the liver were found small islets of normal liver tissue which might be interpreted as an effort to re-establish the normal function of the liver The liver did not contain abnormally large quantities of fat, nor was there an increase of the connective tissue The kidneys still contained some glycogen, especially the glomeruli

After mentioning these facts we give it as our opinion that nothing positive can be said concerning the prognosis of glycogen liver Though optimistic, as a result of personal experience, we do not think we are yet justified in saying that a glycogen liver, after existing for many years during which the condition remains stationary, will become smaller, and that the patient will outgrow his disease, or will turn into a subject of diabetes mellitus The fact that the character of the disease or the size of the liver in the case of *Parnas* and *Wagner*, and also in that of *Worster-Drought*, changed at about puberty, perhaps gives an indication of the existence of a functional disturbance in glycogen disease which is modified in this period

A (passing?) decrease in the circumference of the liver is mentioned in the two cases of *Anderson*, during an attack of whooping-cough in

one child and during a catarrhal icterus with fever in the other. In both cases, strangely enough, the ketonuria *decreased*, and in one of them it returned, after recovery of the patient, to the same marked extent to which it had existed previously.

An important decrease in the size of the liver, and an improvement of the general condition within a relatively short time was noted in one of the cases described by *Ellis*.

8 THERAPY

At present there is no definite therapy for glycogen disease or for glycogen liver. We hope that the future will change this state of affairs, now that many facts have been ascertained from the closer examination of cases of glycogen liver. These facts, perhaps, will be brought into connection with recent discoveries in the field of endocrinology. Thus far, in treating the patients with glycogen liver, the authors have been guided by the following considerations. When the combination hypoglycemia and acetonuria predominated, a diet in which the carbohydrates occupy a very large place and which was particularly poor in fat was recommended. The same was necessary in those cases in which during the first years of life symptoms were present which could be characterized as "hypoglycemic" ones, or in those cases in which, as in our patients, there existed recurrent attacks of vomiting which we now know to have been associated with acetonuria. In both our patients and in some other cases the children showed a great preference for carbohydrates (bread, potatoes), just as if they knew instinctively that such a diet could prevent symptoms of fatigue and nausea. As long as the children kept to their diet these attacks did not return. We could not confirm the opinion that in fulfilling the desire for such large amounts of carbohydrates the accumulation of glycogen would be facilitated.

The fact that frequently there have been indications of the existence of a definite endocrine disturbance has led to the prescription of hormone preparations. In the case of *Parnas* and *Wagner* (if this case may be reckoned with the cases of glycogen liver) thyroid preparations were administered at the start and for some time. Possibly as a result of this treatment the very low fasting blood sugar values became somewhat higher.

Some years ago, we, also, gave our boy thyroid preparations, however without any influence on the fasting blood sugar values or on the ketosis. In view of his bodily condition, which at that time seemed to point to a disturbed pituitary function, we also gave over a long period a preparation of the anterior lobe of the hypophysis, this also had no effect. During recent years we gave to both patients for a long time a gonadotropic hormone (*Pregnyl* of Organon), administered orally, no effect was seen on the fasting blood sugar content, or on the glycogen content of the blood, or on the cholesterol content of the serum.

As the rôle of the hypophysis in the pathogenesis of glycogen liver becomes more and more probable, treatment with injectable preparations of pituitary hormones must be seriously considered. These preparations are now for a greater part available in a more active form than formerly and their effect is less doubtful than that of orally administered preparations. From the discussion of the pathogenesis it appears, that the question which pituitary hormone or which combination of pituitary hormones (in so far as they are available) should be injected in order to mobilize the glycogen and to influence at the same time other metabolic disturbances, is not easily to be answered. In our boy who is now sixteen years old, and has adiposity, small genitals and general delay in sexual development, such a treatment really is urgent. For that reason in the first place treatment with injections of pituitary hormone preparations, containing both the thyreotropic and the gonadotropic hormones, must be tried.

Rauh and *Zelson* gave a course of treatment with epinephrine, because in one of the cases of *von Gierke* hypoplastic adrenals were found. They did not observe any influence on the blood sugar content or on the size of the liver. Prolonged treatment with thyroid also had no influence on the size of the liver or on the fasting blood sugar content. Treatment with liver or liver preparations was totally ineffective in those cases in which it was applied.

Von Gierke recently proposed trying the effect of implantation of a small piece of liver of an animal, of subcutaneous injections of sterile liver pulp, or of injections of blood of diabetics who are not treated with insulin.

The recent researches of *Best* and his co-workers induced us to

examine the influence of oral administration of choline on the ketosis of our patients. From their researches it appeared that a fatty degeneration or an excessive accumulation of fat in the liver produced experimentally, could be totally overcome or greatly diminished by the oral application of choline.

In the cases of glycogen disease which have come to autopsy much fat has sometimes been found in addition to the large amounts of glycogen (first case of *von Gierke*) and especially the cases of *Krakower*. For a long time we gave choline to both our patients and obtained the definite impression that during this time the mean excretion of ketone bodies in both children was much lower than before. However, no influence was noted upon the fasting blood sugar, the glycogen content of the blood, or the cholesterol content.

Unshelm has seen a splendid effect on the size of the liver and on the general condition of the patient as a result of treatment with röntgen rays in a dubious case of glycogen liver. *Harnapp* saw in one case also a temporary effect of irradiation with röntgen-rays upon the size of the liver. However, in a case of glycogen liver treated by *Scharff*, no effect at all was seen from such irradiation either on the size of the liver or on the metabolism. X ray therapy has been recommended in (congenital) hypertrophy of the liver, especially in hypertrophy due to new growths (*Vipplö, Greenwald*)—This method of treatment will not be universally accepted, however, in glycogen disease, for the pathogenesis of the disease offers too many uncertainties, the structure of the liver is surely not the same in all cases, and the general condition in the majority of instances is quite good. A further argument against such a form of treatment is the possibility that it may bring about unfavorable consequences.

9 LITERATURE

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EXTRAPLEURAL PNEUMONOLYSIS IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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The attainment of a successful extrapleural pneumonolysis has been an elusive goal in the surgical therapy of pulmonary tuberculosis ever since the initiation of collapse therapy. Up to the present, there has been no method of extrapleural stripping devised, the use and results of which have withstood careful investigation.

In recent months, a number of reports have emanated from Germany (Graf Schmidt) which makes it opportune to review the subject and to consider the possibilities of the latest advocated procedure, extrapleural pneumothorax and oleothorax.

Artificial pneumothorax is the ideal method of collapse therapy because it is simple and effective. Phrenic operations have their field of usefulness and thoracoplasty has been proven a dependable therapeutic procedure. Unfortunately, there are many cases where the above procedures either cannot be used or are of no value.

The manifestations of pulmonary tuberculosis are so varied that it is of great importance to enlarge the field of operative methods so that there may be some type of therapy to offer to the patient whose prognosis will be poor without active treatment.

The greatest problem in collapse therapy is the patient with a bilateral cavernous lesion. In the great majority of these, the prognosis being poor, any good therapeutic procedure which they can withstand will have a large field of usefulness. Many bilateral cases show a tendency to fibrosis and healing. If some aid can be given to these natural forces, great benefit will ensue. If pneumothorax is not possible because of adhesions, and thoracoplasty is contraindicated because of the bilaterality of the lesion, a minor procedure, such as

extrapleural pneumonolysis may be well borne and effective in converting the case to a unilateral one

Extrapleural pneumonolysis has for years been the procedure of choice when it was considered inadvisable to perform a thoracoplasty. Unfortunately, the results obtained were not satisfactory, due to the fact that either the disease was too widespread or that the procedure did not accomplish its intended purpose.

Extrapleural pneumonolysis has failed in the main because of the inability to maintain the collapse produced at the time of operation. In complete artificial pneumothorax, the collapse of the lung can be maintained as desired, except in those cases in which complications arise. Phrenic avulsion produces a collapse which remains permanent. Temporary diaphragmatic paralysis produced by phrenic crush can be repeated and maintained for a number of six month periods or can be converted into a permanent paralysis. Thoracoplasty gives an enduring collapse. In extrapleural pneumonolysis, the frequent occurrence of loss of collapse is one of the great problems to be solved.

ANATOMY

The anatomical structure which has a prime significance in the performance of an extrapleural pneumonolysis is the endothoracic fascia. The presence of the endothoracic fascia, as a continuous membrane in the chest cavity, makes the performance of a pneumonolysis possible and also supplies a layer of tissue on the inner surface of the cavity wall which later permits of the introduction of air.

Mertens, in 1914, made anatomical studies on fifteen cadavers and found that the endothoracic fascia was a continuous thin membrane covering the entire bony cage and diaphragm. Over the intercostal spaces, it can be definitely found as a fascial sheath, but over the posterior periosteum covering the ribs, it tends to lose its identity and is partially merged into the periosteal layer. It is separated from the costal pleura by a narrow layer of connective tissue. Over the diaphragm it is so adherent to the parietal pleura that they cannot be separated. The apex of the lung, together with the endothoracic fascia, periosteum and intercostal musculature, is connected by numerous ligaments and fibrous tissue bundles to the vertebrae, the subclavian vein and brachial plexus. This system of muscles, ligaments

and fibrous bands which suspend the pleural dome has been described in detail by Zuckerlandl, Sebileau and Truffert

Ordinarily, these extensions do not come into consideration in the performance of an extrapleural pneumonolysis because theoretically, this is done inside of the endothoracic fascia. However, long standing pulmonary disease which causes a synechia between the visceral and parietal pleura will also cause an inflammatory lesion of the connective tissue layer between the parietal pleura and the endothoracic fascia. When these adhesions are especially dense and fibrotic, it may be impossible to separate the parietal pleura from the fascial membrane. In about 5% of the cases it is mechanically impossible to perform an extrapleural pneumonolysis because of these adhesions.

TECHNIQUE

As a rule, an extrapleural pneumonolysis is performed for the purpose of simple apicolysis, insertion of a Plombe, or for the maintenance of an extrapleural pneumothorax. The technique of the procedure is practically the same in all cases. When the approach is made anteriorly, a horizontal incision is made over the anterior end of the second or third rib. Local anesthesia is used. The periosteum is carefully stripped from the rib and a piece of rib removed. Incision through the posterior layer of the periosteum is then made and the space between the parietal pleura and the endothoracic fascia identified. By means of finger manipulation or sponges, the lung is freed over the apex and as far down anteriorly and posteriorly as is necessary. The only place that difficult adhesions are encountered is at the apex. Closure is carefully done with exact suturing of the periosteum, musculature and skin. The absence of a section of rib causes a weakness in the thoracic wall through which material inserted, as a Plombe, may be extruded.

Krampf and O'Brien replaced the piece of resected rib and sutured it in position in order to increase the firmness of the chest wall. Maendl goes a step further and makes a flap of a piece of rib so that it is merely turned aside during the operation and then replaced.

Eloesser has found it possible to perform a pneumonolysis by the anterior approach without removal of a piece of rib. By simple

intercostal incision, he is able to satisfactorily free the lung. Romanis and Sellors also use this technique. Stocklin obtains sufficient exposure by separating two ribs at their cartilages.

Because of the postoperative weakness of the anterior chest wall, the posterior approach has become the most popular. The thick layer of muscles over the posterior thoracic wall forms an excellent bulwark.

For the posterior approach, a curved incision is made from the second to the sixth ribs, midway between the scapula and the spinous processes. Vidakovits places the incision on the edge of the scapula so that the scar will be practically invisible. The soft tissues are incised, followed by the trapezius and the rhomboideus major and minor muscles. The scapula is then retracted as far laterally as possible, exposing the serratus posticus superior and the underlying ribs. The serratus posticus is bluntly separated along the lower edge of the fourth rib and retracted upward. It is important to keep this muscle intact in order to secure a good closure. The periosteum over the fourth rib is then incised and stripped carefully. Five to six centimeters of this rib are then resected close to the spine.

Following this, the intercostal nerve is isolated and resected, and the intercostal vessels doubly ligated and excised. Blunt separation of the fibers of the internal intercostal muscle then exposes the endothoracic fascia and the parietal pleura. The finger is gradually inserted into the space between these two layers and separation of the lung from the chest wall is carried out. An occasional dense adhesion may have to be clamped and coagulated before cutting. The entire space must be tamponed at intervals with hot gauze packings to control oozing. Through this posterior incision, the entire apex of the lung may be stripped as far as the hilum. The stripping must be done with extreme care along the vertebral side. When all bleeding has been controlled, a Plombe may be inserted, or the space left empty, as desired. A light carrier is of great advantage in inspecting the depths of the space and frequently adhesions near the apex may have to be freed with a sharp separator. The closure should be carefully done, first approximating the intercostal musculature and the periosteum, if it has been incised, then suturing the muscle bundles of the serratus

posticus, and finally, the rhomboidi and trapezius muscles, subcutaneous tissue and skin

Approach through the axillary region has also been attempted but has not been fruitful because of the difficulty in reaching the apex of the lung and also because of the paucity of muscles over this part of the thorax. Kremer removes the periosteum from the inner surface of the second and third ribs and allows it to remain attached to the collapsed lung. He believes this provides a good base for the Plombe, if one is used, and will allow the formation of new osseous tissue to maintain the lung in its collapsed state. He also advocates this technique for extrapleural pneumothorax.

Graf inserts a tube through a stab wound in the second intercostal space in order to inflate with air for extrapleural pneumothorax. Schmidt does not drain but aspirates any fluid which forms. He uses the area supplied by the fourth intercostal nerve for all needle punctures. This nerve having been resected, the area is anaesthetic.

Other forms of apicolysis, such as Lauwers, are frequently combined with a resection of a piece of the first or second rib. Naturally, any apicolysis or pneumonolysis which is used in conjunction with a thoracoplasty is much simpler to perform because the exposure is facilitated by the previous resection of large segments of ribs. Coffey, through a supraclavicular incision, resects part of the first rib, the scalenus anticus muscle, and the phrenic nerve in conjunction with an apicolysis. Other modifications have been proposed by Jacobovici, Mallet Guy, Gregoire, Loeschke and Rost, and Antelava.

INDICATIONS

As a general rule, the indications for extrapleural pneumonolysis are the same regardless of whether it be a simple apicolysis, a Plombe or an extrapleural pneumothorax or oleothorax.

Extrapleural pneumonolysis is never indicated as a substitute for thoracoplasty. The low mortality of present day partial upper thoracoplasty, together with its high percentage of favorable results, makes it the procedure par excellence for unilateral, apical cavity disease which cannot be treated by either phrenic operation or pneumothorax. If there is some extrapulmonary complication, such as cardiac or renal disease, which makes it unlikely that the patient will be

able to withstand a thoracoplasty, then extrapleural pneumonolysis may be tried. Also, if the age or general condition of the patient contraindicates a thoracoplasty, extrapleural pneumonolysis is a non-shocking procedure which can be well borne.

Where there is apical disease on one side and extensive pulmonary involvement on the other, an extrapleural pneumonolysis is indicated to control the apical disease, in order that a thoracoplasty or pneumothorax may be used later over the contralateral lung. Where there is persistent bleeding known to come from one apex, extrapleural pneumonolysis is an effective means of controlling the hemoptysis if pneumothorax and diaphragmatic paralysis have been unavailing. Where a cavity still persists after extensive rib resections, pneumonolysis is an excellent measure to complete the obliteration of the vomica.

Where the cavity is so large that thoracoplasty does not offer a fair chance of closure, a preliminary pneumonolysis may reduce its size sufficiently so that later thoracoplasty can be effectual (Head-Michelsson).

METHOD OF ACTION OF EXTRAPLEURAL PNEUMONOLYSIS

The prime factor in the performance of a pneumonolysis is, as the name indicates, the separation of the lung from its attachment to the chest wall. The freeing of the cavity walls allows the normal healing factors to exert their effect and permit fibrosis and contraction to proceed unhampered.

The advocates of simple apicolysis believe that the operative manipulation, as well as the effusion which forms, initiates a fibrosis in the pleural layers which extends into the pulmonary tissue and has a direct effect upon the tuberculous process. Such a fibrosis is probably also encouraged by the use of either temporary or permanent tampons.

Lauwers feels that the relation of bronchial closure to obliteration of cavities is undoubtedly an important one. It is evident that this may occur during the release of the apex of the lung and the consequent change in position which occurs.

The pressure exerted upon the collapsed apex is of little importance except in the maintenance of the collapse. The best results in "Plombierung" are obtained with small amounts of paraffin. Extra-

pleural pneumothorax does not have to be maintained under high pressures. In the "Einstülpungs Plombe," the pressure of the weight of paraffin is used to invert the upper margin of the cavity into the lower. It must not be forgotten that in thick-walled cavities, the blood supply is markedly diminished. Any great pressure on such an area will cause a pressure necrosis of the cavity wall and a perforation. In the use of rubber balloon tampons in suprapariosteal subcostal pneumonolysis, Alexander felt that the marked pressure on the periosteum was a factor in inhibiting the formation of new osseous tissue.

As in practically all other forms of surgical collapse therapy, pressure is not a factor. If the lung is freed from its fixed points, which prevent concentric retraction and fibrosis, then these forces are allowed to exert their natural tendency to healing.

EFFECT ON RESPIRATION

It is the negligible effect which extrapleural pneumonolysis has upon the respiratory function which makes it a procedure suitable for sick patients with extensive disease and low vital capacity. Even though an apical thoracoplasty is confined to the upper three ribs, there is probably very little respiration (during the postoperative period) performed by the remainder of the operated lung. With pneumonolysis, on the other hand, the collapse is a very selective one, and the amount of rib removed so small that respiration of the lower lobe may be carried on without postoperative pain.

Castelli used the thoracopneumograph of Baglioni to measure the effect of the insertion of paraffin on the movements of the thorax. He found that only the movement of the apex on the operated side was diminished and the remainder of the respiratory mechanism was unimpaired.

DIAPHRAGMATIC PARALYSIS AND EXTRAPLEURAL PNEUMONOLYSIS

In view of the fact that extrapleural pneumonolysis was usually performed for a small sized apical lesion, it was not uncommon to find that diaphragmatic paralysis had first been tried as a method of collapse therapy. Because of the use of phrenic avulsion at that time, the diaphragmatic paralysis was a permanent one and therefore was still present at the time of the pneumonolysis. Today, if one

were to try diaphragmatic paralysis for control of the apical lesion, a temporary paralysis would be instituted by means of phrenic crush. Should this be of no avail and pneumonolysis then decided upon, the function of the diaphragm would have returned. In the early days of surgical therapy for pulmonary tuberculosis, diaphragmatic paralysis was frequently performed prior to upper thoracoplasty and extrapleural pneumonolysis in the belief that it was a method of protection for the lower lobe and would prevent the occurrence of post-operative pneumonia, either tuberculous or non-tuberculous.

Nissen used diaphragmatic paralysis for prevention of aspiration and Kremer advised it not only for such a purpose but also to reduce the size of a cavity. Sattler felt that a paralyzed, raised diaphragm was an aid in keeping the paraffin mass in its correct position. After considerable experience had been accumulated and experimental work carried out on the value of diaphragmatic paralysis as a preventive of postoperative pneumonia, it was evident that the early idea had been fallacious.

Holst and Semb made a very careful x-ray study of post-operative atelectasis after apical thoracoplasties and found that this condition occurs much more frequently in the presence of a paralyzed diaphragm than when this muscle is functioning normally. In as much as atelectasis is a predisposing cause of pneumonia, the advantages of having an intact diaphragm are evident.

The evidence is in favor of the diaphragm being a very large component in the act of cough and expectoration and therefore its action in aiding to remove aspirated mucous and pus from the lower lobe bronchi is of great importance. It is true that experimentally and clinically, during the course of a tuberculous bacteremia, there is less seeding of the pulmonary tissues adjacent to a paralyzed diaphragm. But the etiology of postoperative pneumonia is bronchogenous in the great percentage of cases and only rarely hematogenous.

"SIMPLE" EXTRAPLEURAL PNEUMONOLYSIS

In 1893, Tuffier performed the first simple pneumonolysis in the extrapleural plane but inserted nothing to maintain the dead space obtained. It was not attempted by others until F. Jessen, in 1913, reported six cases with good results. He had observed a cure in one Plombe case even though the paraffin had been extruded and there-

fore decided to attempt simple pneumonolysis. He believed that if the separation of the lung were extensive enough, and the disease process a suitable one for this type of therapy, healing could be obtained. The same author, in 1916, also reported the use of a somewhat different simple pneumonolysis. After the lung had been freed to the desired extent, the wound was left open so that the pressure over the collapsed lung remained the same as the intratracheal pressure. He felt that this would prevent reexpansion of the pulmonary segment.

Harald Jessen, in reviewing 15 years of collapse therapy, in 1927, cited 8 cases of simple apicolysis. Four were cured, (one after 11 years, 3 after 12 years) one was well after four years, one unimproved and 2 dead. Thearle, in 1926, found that simple pneumonolysis was of no value because the lung always reexpanded due to the granulation tissue which eventually filled the dead space.

Lauwers, in 1928, described the operation which came to be known as the "Lauwers' Apicolysis." Through an anterior supraclavicular approach, the first rib was resected and the apex of the lung freed from its attachments to the ligaments which suspend it. At the same time, the scalenus anticus muscle was severed and the phrenic nerve avulsed. He used no compressing material but felt that the diseased area of lung had lost its elasticity and would not reexpand.

Frangenheim, two years later, reported his experiences with Lauwers' apicolysis but undoubtedly found that there was a tendency for the lung to reexpand for he suggested the injection of air or oil to prevent such an occurrence. Bremer, in 1931, reported 15 cases of apicolysis with a few good results (6 cavities closed). He felt that whatever healing was obtained was not only due to the temporary collapse but also to a fibrosis which was initiated by the operative procedure and the postoperative serosanguineous exudate. The fibrous reaction, beginning in the parietal pleura, later permeated the pulmonary parenchyma.

Uhlenbruch reported 2 good results out of 9 cases operated with the Lauwers' technique. Omodei Zorini, in 1932, because of frequent lower lobe spreads after the insertion of a paraffin Plombe, advocated simple apicolysis which apparently was not followed by complications. In 1933, he reported 17 cases with 7 closures of cavity and negative sputum. Jachia advocated total extrapleural pneumonolysis over the entire lung with the hope that the effusion which formed would

maintain the pulmonary collapse. When this did not occur, he injected a mixture of the patient's blood and lipiodol, or used gas or a balloon. He felt that the walls of the extrapleural space could become sufficiently fibrotic so that air could be injected later.

Kremer advocated the use of simple apicolysis in cases in which pneumothorax did not collapse an apical cavity because of broad adhesions. He performed the procedure in the presence of the incomplete pneumothorax, which was maintained after operation. Monaldi also reported 15 cases with conversion of sputum in 6, and Mantan has operated on 22 cases with 7 permanent cures.

Joannides, in 1934, recommended what he called extra-intrapleural supraclavicular apicolysis. Through an incision above the clavicle, (such as for phrenicectomy) the phrenic nerve was avulsed, the scalenus anticus divided and the cupola of the lung depressed by finger manipulation. This was performed in the extrapleural plane as far as the fourth rib posteriorly and the second, anteriorly. This was also carried out for adherent apical cavities with incomplete pneumothorax. The pneumothorax cavity may be entered or held intact as desired. Joannides had not tried this procedure on patients but from his experiments on animals and cadavers, he felt that it was feasible.

Michelson, in 1935, reported satisfactory results with 20 simple apicolyses. He chose this operation rather than the insertion of a Plombe because of the many complications which accompanied the latter. He did not cause a diaphragmatic paralysis before separating the apex because he felt that an intact diaphragm was a vital part of the act of expectoration and was therefore necessary to prevent spreads to the lower lobe.

Michelson has also proposed the use of apicolysis for the purpose of decreasing the size of a giant cavity and lessening the amount of sputum before a thoracoplasty. Realizing that an apicolysis in itself would not close a large cavity, he performed a pneumonolysis over the apex, with resection of part of the first rib. At a second operation, when thoracoplasty was performed, the danger of aspiration pneumonia was lessened and the chances of closing the cavity increased.

Recently, (1936) Lauwers has sought to cause a fixation of the lung after it has been collapsed by his method of apicolysis. After freeing the lung, he applies a mixture of alcohol (5 parts), chloroform (3 parts)

and acetic acid (2 parts) to the pleural surface. Experiments on animals have shown that this application results in a marked pleural fibrosis with extension of the process into the pulmonary parenchyma

EXTRAPLEURAL PNEUMONOLYSIS WITH TEMPORARY TAMPONADE

Knowing that the normal tendency of the lung is to reexpand after pneumonolysis, various methods have been used temporarily to preserve the collapse obtained

Gauze tamponade has been the favorite medium for this procedure. Schlange, in 1907, used gauze packings following pneumonolysis to successfully control pulmonary hemorrhage. Eizaguirre, in 1922, because of complications from both fat and paraffin, used gauze packings after pneumonolysis. Bruns (1931) had used various types of gauze, plain, iodoform, and finally used vaseline gauze containing 0.5 per cent iodoform and 0.5 per cent bismuth carbonate. He was unable to maintain the extrapleural space even with the most diligent postoperative care, the lung would eventually reexpand and later thoracoplasty was necessary.

Simenstein has also reported the successful control of hemorrhage in 5 out of 6 cases by extrapleural pneumonolysis and gauze tamponade. Gauze tamponades are frequently used where pneumonolysis is combined with thoracoplasty.

Other media have been tried in order to maintain a temporary collapse in the hope that either sufficient fibrosis would occur to prevent reexpansion or that the pulmonary lesion would heal during this period. Lilienthal has suggested the use of wire mesh and has used crumpled rubber dam to great advantage. The dam will apparently double or treble the size of the extrapleural space made at operation and may be removed at the end of approximately 5 days and be replaced by a drainage tube. Lilienthal uses this method of apicolysis in conjunction with a first stage thoracoplasty.

Rubber balloons have also been used for temporary pressure within the extrapleural space. When made of thin material, they will take the shape of the space and exert uniform pressure throughout. Gwerder and Schoenlank, in 1913, used this method experimentally in animals and felt that it caused practically no reaction and had the greatest similarity to pneumothorax. Kroh inserted an inflated rubber glove and maintained it in place for 2 weeks, following it with

gauze packing One case was for a post-pneumonic gangrene of the upper lobe He performed an extrapleural pneumonolysis and then inserted a thin rubber glove which he inflated He also tried the same method on a case of pulmonary tuberculosis, with an apparent cure in both Maisel also experimented in animals with a rubber balloon Baer used a rubber balloon in one case in which he had to remove a paraffin Plombe After removal of the balloon, he found that there still was marked paradoxical respiration

de Fonzo inserted a rubber balloon after the usual apicolysis and then buried the connecting tube of the balloon subcutaneously The tube was then exposed at intervals and air reinjected into the balloon He claimed good results in 2 cases but the follow up period was short Romanis and Sellors also attempted to use rubber balloons but found that they could not be left in place indefinitely

Oughterson and Harvey used a rubber balloon as follows a number of ribs were denuded of periosteum and muscles and these tissues pushed inward, leaving an extrafascial space between the ribs and the collapsed lung A rubber balloon was then inserted between the ribs and inflated to fill the dead space The bag was kept inflated until new bone had formed from the periosteum, which had remained attached to the collapsed lung The bag and denuded ribs were then removed Apparently, this method was successful in animals but when Alexander and Haight attempted it clinically, they found that even after 3 months, sufficient new bone had not been formed to prevent marked paradoxical respiration with all its disturbing symptoms and complications They felt that this was due to the pressure of the bag on the periosteum, plus low grade infection

EXTRAPLEURAL PNEUMONOLYSIS WITH PERMANENT TAMPONADE

Fat and paraffin have been the two chief media used as permanent tampons after pneumonolysis has been performed Fat was first used but paraffin became the most widely utilized

Fat

Tuffier, in 1911, was the first to describe the insertion of fat into the extrapleural space which he made by separating the lung in the extrapleural plane Wilms also used fat transplants to increase the collapse obtained at the time of performing a thoracoplasty The

Wilms' Thoracoplasty, or "Pfeilresektion," entailed the removal of only small pieces of rib and the fat was inserted to aid in pulmonary compression. In 5 cases, the fat healed successfully. Bull, in 1920, also reported the use of fat to fill the space formed by the extrapleural pneumonolysis which he performed in order to facilitate the resection of the first and second ribs. Steenstrup reported two successful fat transplants from the abdominal wall, one in conjunction with a thoracoplasty and the other as an independent operation.

In 1926, Tuffier reported on 57 extrapleural pneumonolyses performed since 1891 upon 53 patients. 44 were for tuberculosis, and 11 for other pulmonary diseases. Fat was used 33 times, paraffin 8 times, omentum 8 times, and a lipoma once. Only twice was the mass ejected. A six to nine years follow up showed that 17 were fully cured and 18 had died of tuberculosis. In seven, a fistula had formed. Lilienthal has also used fat transplants with success. Edwards reported the use of 5 fat grafts, three in conjunction with thoracoplasty, one with intrapleural pneumothorax and one as an independent operation, but this case needed a subsequent thoracoplasty. All the grafts healed successfully.

Zamboni (cited by Jehn) used red rubber sponge in the extrapleural space of animals and found that it not only healed by first intention but also became organized by the growth of connective tissue. Schulze experimented with natural bath sponge and found, if treated with 5 per cent tannic acid for 1 to 3 days, it formed a medium which healed without reaction and was slowly surrounded by a connective tissue capsule.

Muscle

Besides paraffin and fat, pedicled muscle flaps have been used to maintain the collapse attained by pneumonolysis. The value of pedicled flaps, usually of the pectoralis major and minor muscles, is that they are living grafts and not irritating. Their disadvantages are that they can only be used for a small extrapleural space and that they usually shrink and become fibrotic after a period of time.

Shivers, in 1917, suggested both anterior and posterior pedicled muscle flaps in conjunction with thoracoplasty to aid in apical collapse. Archibald also used pectoralis flaps through an anterior incision to reenforce an apicolysis. de Winter used muscle flaps in conjunction with resection of the second rib and apicolysis. Gossaerts

reported on 36 cases of pneumonolysis with muscle transplant. There were 7 postoperative deaths, but in 10 cases the outcome was satisfactory. Davies, in 1932, reported his satisfaction with the use of pectoralis flaps to maintain the extrapleural space.

Alexander, in 1934, reported the use of muscle flaps in a type of pneumonolysis which is not a typical extrapleural pneumonolysis. He called his procedure "supraperiosteal and subcostal pneumonolysis," and had first used it in 1927. The second and third ribs were stripped of their periosteum and intercostal musculature through an anterior incision. The pneumonolysis thereby performed was not between the costal pleura and endothoracic fascia, but was external to the periosteum and intercostal muscles, which were left attached to the lung. The pectoralis muscles had been prepared in a pedicled flap and were drawn through the intercostal space and fixed into the cavity thus formed. The denuded ribs did not lose their vitality but could be removed at a later operation if necessary. This type of pneumonolysis was similar to that used by Oughterson and Haight experimentally, and by Alexander with rubber balloon compression. In a series of 1200 patients treated by various surgical measures, Alexander used this procedure only seven times during a period of seven years. One was for a non-tuberculous abscess which resulted in a cure. In three of the six tuberculous cases, the operation was done preliminary to thoracoplasty. One of the remaining three died as a result of the operation. One was improved and one apparently cured. Churchill reported the use of Alexander's procedure in three cases but his early good results did not persist, due, in his opinion, to shrinkage of the muscle flap.

Kulczyk and Norvotny experimented with muscle grafts in rabbits and found that they started to degenerate in a few hours and were removed by phagocytosis. It is likely that they experimented with free grafts and not pedicled flaps.

Haberlin has also used the de Winter method of anterior pneumonolysis with muscle flap insertion. At a later date, he performs a posterior rib resection with excellent results. Stegemann, in 1937, reported the use of extrapleural pneumonolysis through an axillary approach with resection of the third rib. After the lung had been freed, he sutured the pectoralis major muscle over the top of the collapsed lung to prevent reexpansion.

Paraffin

Baer, in 1913, suggested and used a paraffin mixture as a Plombe to maintain the space created by extrapleural pneumonolysis. Many others claimed that paraffin was not the ideal medium for permanent plombage, nevertheless, in spite of many attempts to find a substitute, paraffin has remained the only material which has given satisfactory results.

The technique of the pneumonolysis is the same as that previously described. After the extrapleural space has been prepared and all oozing has been controlled, the paraffin is inserted. Baer's original paraffin mixture was composed as follows: 75 cc of paraffin, with a melting point of 58°C , is mixed with 25 cc of paraffin with a melting point of $43-44^{\circ}\text{C}$. To this is added 1 cc of bismuth carbonate and 0.05 cc. of vioform. The paraffin should be sterilized for one hour on two successive days. At the time of insertion, the mass is warmed until it is pliable and is inserted through the thoracotomy opening in small sausage shaped masses. The amount inserted depends upon the size of the space to be maintained. This may vary from 100 to 1000 cc. Winternitz, Scholz, Kremer, Neddermeyer, Charrier, Tallyaroth, Starcke, Gilbert, Perera, Truchaud and Behrens, believe that "Plombe" should be limited to 300 to 400 cc. in size or even less, and feel that larger masses are the cause of "wandering of the Plombe," and perforation into the cavity. Hudson never uses more than 150 cc and does not attempt to fill the extrapleural space and has not seen suppuration or perforation in 50 cases.

Hauke, Nissen, Sauerbruch and others have used Plombe as large as 1000 cc and Henschen has even used 1800 cc, but undoubtedly the need for such large masses can only be found in the treatment of extremely large cavities, and the ideal indications for pneumonolysis with Plombe limit the procedure to cavities not exceeding 4-5 cm.

Various attempts have been made to find a medium which will surpass the paraffin mixture. Lebsche omitted the bismuth and vioform from the paraffin and added numerous metal pellets which would demonstrate the paraffin mass in the x-ray and not obscure the pulmonary field. One objection to paraffin is that it causes a foreign body reaction and becomes encapsulated. The ideal substance would be an unabsorbable one which would not be irritating and would have

connective tissue grow into it from the surrounding structures Eden used "Humanol," a fatty oil Tuffier used "Beck's Paste"

Brauer, in 1928, suggested "Vivocoll," a beef serum activated with calcium salts It has the property of stopping oozing and serous secretions from the tissues Heine tried "Vivocoll" to which he added such things as paraffin powder, calcium, asbestos powder, small pieces of cartilage, splenic capsule, periosteum and skin He sought a substance which could be poured into the extrapleural space thereby filling all the crevices, leaving no dead space Katzenstein added cow's milk, casein and 0.02 per cent melted Rivanol to Vivocoll and found that this mixture healed both intra- and extrapleurally without reaction and became surrounded by connective tissue

P. Schmidt, experimenting with wax-gelatine and gelatine plus stearin or cellulose, felt that the first was equally as good as paraffin but the others were too irritating He found definite connective tissue growth into the wax-gelatine Scholz, in three cases tried rubber sponge soaked in paraffin or Vivocoll but had a severe local reaction in all three He also tried a "granugenol paraffin mixture" in three cases but there was a marked reaction and the mixture was extruded Rehn, in 1937, seeking a substance to cause fixation of the mediastinum, used "Polyvinylalkohol" This preparation is a fluid at 45° to 50°C but at body temperature assumes a rubber-like consistency It is sterilizable, may be poured or injected, heals well, and is very slowly absorbed This substance when injected, produces a marked fixation of the mediastinum, and Rehn felt that if inserted into the space produced by an extrapleural pneumonolysis, it would act as an excellent Plombe and cause fixation of the lung in its collapsed state All the attempts to find a better substance than paraffin have been futile

There have been various refinements in technique proposed for the pneumonolytic procedure so as to lessen the failures and complications occurring with paraffin Plombe Kremer does not perform the pneumonolysis strictly in the extrapleural plane He also removes the posterior periosteum from the second and third ribs and allows it to remain attached to the collapsed lung He believes that this added covering to the lung prevents perforations into the pulmonary cavity In 125 cases he has not seen a perforation within the first three months

Furthermore, this periosteum will form new bone and prevent future pulmonary reexpansion. Sachs also uses this method of pneumonolysis. Kremer even advised this technique for extrapleural pneumothorax but because the separation is not in a distinct fascial plane there would be danger of interstitial emphysema.

Backer-Grondahl, who feels that the pneumonolysis is the most important part of the procedure and believes that it must be carried exactly to the correct limits, uses x-rays during the operation to determine when the lung has been stripped sufficiently. He inserts a small rubber balloon into the space made at operation, inflates the balloon, and takes an x-ray plate. The balloon distinctly outlines the extrapleural space and the surgeon can tell when he has separated the lung sufficiently.

The amount of lung separation that is attained before the insertion of a paraffin mass is of great importance. There must be a complete obliteration of the entire pleural space or else perforation into the pleura is likely to occur. In thick-walled cavities the lung should not be freed below the level of the cavity for the vomica is then pushed downward into healthy lung tissues without being compressed.

In order to compress a thick-walled cavity, Hauke uses what he calls an "Einstülpung's Plombe." He frees the lung only over the upper half of the cavity, leaving the lower limits fixed. Then by placing the paraffin over the apex of the cavity, he hopes to have the upper half inverted into the lower half, much in the manner as one would invert one half of a soft rubber ball by squeezing.

Cavities do not necessarily have to be compressed from above downward but may also be treated by means of a Plombe exerting its action from behind. The results are not as good when paraffin is inserted anteriorly, or through the axilla, as when it is placed on top of, or posterior to the lesion.

Ulrici and Thomsen and Alexander used multiple Plombe on the same side with good results. If an anteriorly placed mass of paraffin does not succeed in closing a cavity, a supplementary posterior insertion may be performed, and vice versa.

The operation of extrapleural pneumonolysis and insertion of paraffin is a minor, non shocking procedure and may be used in very sick patients with a small operative mortality. Winternitz reported

a 3 per cent early mortality, Sattler 3 per cent, Beitz 3 per cent, Ostrowski 4 per cent, Steele 5 per cent, Starke 4 per cent, Stoiko $1\frac{1}{2}$ per cent, Huber 8 per cent, Nissen 2-3 per cent, and Kremer 6 per cent.

The frequent occurrence of early or late complications is the objection to the procedure. Paraffin is a foreign body and acts as such. An exudate occurs in practically every case and may have to be aspirated. Eiselsberg noted a rise in temperature in about two-thirds of the cases. This did not return to normal for eight to ten days. He felt that this was due to increased absorption from the compressed areas.

Head, in 528 cases, listed the complications as follows:

Lung torn at operation	10 (1.8%)
Pleura torn at operation	11 (2.0%)
Infection of pack	12 (2.2%)
Extrusion of pack	7 (1.5%)
Perforation of pack into cavity	18 (3.3%)
Pack slipped	6 (1.1%)
Pneumonia or atelectasis	13 (2.3%)
Operative deaths	21 (3.8%)

Accidents occurring during operation are uncommon but tears into the tuberculous cavity, openings into the pleura and hemorrhage from branches of the subclavian vessels have been reported. A Horner's syndrome, due to injury to the cervical sympathetic, was observed by Backer-Grondahl.

Tuberculous spreads to the lower lobes have occurred much less frequently than in selective thoracoplasty, probably due to the fact that the Plombe, by reason of its weight, prevents paradoxical respiration.

Infection of the paraffin bed has been reported in various frequencies by different surgeons. Eiselsberg claimed that 33 per cent became infected and Sauerbruch, in 1914, reported 25 per cent of infection and extrusions in his first series of 27 cases. Denk reported 65 per cent infections. Hauke and Walzel, 3 and 2 per cent respectively. Winternitz and Hudson had no infections and Kremer saw only stitch abscesses. Diehl inserted a Plombe in one case and later removed it to perform a thoracoplasty. After operation, a tuberculous infection of the previous paraffin bed occurred.

Extrusion of the paraffin through the skin incision may occur without the presence of infection. This occurs in 1 to 5 per cent of cases.

The paraffin may not be extruded in toto, the fistula may close after part has been evacuated and the remainder heal in situ

Slipping or wandering of the paraffin mass has been observed by Denk in 13 per cent of cases. Where only small amounts of paraffin are used, this complication rarely occurs. The presence of firm pleural adhesions will also tend to prevent a migration of the Plombe.

Pressure symptoms have been observed by those surgeons using large Plombe. Denk experienced it in 16 per cent of his cases. Sauerbruch has seen it occasionally and Huber saw the mass actually perforate into the mediastinum. When pressure occurs, the paraffin must be removed immediately.

Early and late perforations into the tuberculous cavity are the most frequent and annoying complications of this operative procedure. Once again the size of the Plombe and the character of the pulmonary pathology are of great importance. Where there is active disease around the cavity wall, the danger of perforation is increased. When the perforation occurs early, the paraffin must be removed at once because a severe infection of the Plombe bed usually occurs. When it occurs late, (Sauerbruch has observed it after eleven years) the danger of infection is slight. Part or all of the paraffin may be expectorated and the fistula may even close. Occasionally, such an occurrence will have no untoward effect, especially if the pulmonary tuberculosis has healed.

Hudson, who uses small Plombe, had no perforations in 50 cases. Kremer saw only two (12 weeks and 6 months) in 125 cases and felt that this was due to his technique of separating periosteum with lung. Hauke saw 2.5 per cent perforations, all in cases with active disease around the cavity. Steele, Beitz and Walzel had 7 to 8 per cent perforations, Winternitz 11 per cent, Denk 13 per cent, and Neddermeyer 18 per cent. When a late perforation occurs after the pulmonary lesion has undergone fibrosis and the general condition of the patient has improved, a thoracoplasty may be performed to aid in maintaining the collapse and to close the fistula. Lapin has reported a perforation of the paraffin into the esophagus.

Bilateral Plombe

In view of the fact that bilateral apical thoracoplasties have been successfully completed, it is not surprising to find that bilateral

Plombe have been used. Steele reported five cases performed at Alexander's Clinic. Behrens has reported three cases. Jehn reported a cure in one case. Cetrangolo and Huber have each reported single cases.

A statistical collection of the results of paraffin Plombe is difficult to obtain. Few large series have been reported upon and as is usual in most reports on the treatment of tuberculosis, the criteria of cure are very variable. Sauerbruch states that the procedure has been used over 1000 times in his clinic but has not published the results. Many reports only cover a short follow-up period. In view of the fact that the operation is indicated only when more effective means of collapse therapy are not possible, one cannot expect the end results to be exceptional.

Head, in 1934, collected 317 cases from 13 authors. Follow-up showed 101 negative sputa, sixteen postoperative deaths and twenty later deaths. In 89 unilateral cases, 49 were considered as cured.

Table 1 gives the results as reported by authors in 1144 cases. Most of Head's collected cases are included, as well as many others from the literature. There are probably some reduplications because the same cases may have been reported by more than one author, for instance, both the physician and surgeon reporting a series from the same sanatorium. Follow-up period in many cases is short and it is difficult to evaluate the results where differentiation is not made between severe bilateral cases and ideal unilateral cases.

PNEUMONOLYSIS IN CONJUNCTION WITH THORACOPLASTY

In the very early history of thoracoplasty, it was recognized by Garre and Quincke that a pneumonolysis and separation of adhesions would be a distinct advantage in the performance of a rib resection. The early thoracoplasties did not always include resection of the first rib and therefore Friedrich suggested an apicolysis to free the pulmonary apex from its attachment to the first rib.

Bull performed a pneumonolysis in conjunction with a thoracoplasty because he found that it facilitated the removal of the first and second rib. Stocklin also utilized pneumonolysis to increase the collapse obtained by rib resection. Sauerbruch has always advocated the use of pneumonolysis as a part of thoracoplasty in indicated cases. Wilms

TABLE 1

NAME	YEAR REPORTED	NUMBER CASES	NUMBER FOLLOWED	TIME OF FOLLOW-UP	SPUTUM NEGATIVE	IMPROVED	SAME	WORE	DEAD
Sauerbruch	1920	40	37	1½-2½ years	7	5	1	19	5
Stocklin	1921	13	13			5	5	1	2
Ranzi	1922	10	10			4	2		4
Brunner	1924	10	10		1	5			4
Gergely	1929	10	10		3	5	1	1	
H Alexander	1929	10	10		4	4	2		
Hauke	1929	32	32		10	9	8		5
Orszagh	1929	10	10		4	3	1	2	
Starcke	1930	50	50		10				
W Sachs	1930	8	8		3		5		
Walzel	1930	106	106	1 year	42				14*
Denk	1931	30	23		2	10	4		7
Waltuch	1931	15	15	1-2 years	7	2	4		2
Roloff	1931	10	10	2-5 years	2		4		4
Winternitz	1932	106	79		25				1†
Kremer	1932	52	22	1-3 years	10		8		3
Stolko	1932	80	61	½-5½ years	27	17	8	2	5
Huber	1932	25	11	10 years	1	2			8
Iamandi	1932	5	5		1		4		
Randolph	1932	9	9	1-7 months		7			2
Behrens	1933	38	38		22	1	10		5
Sattler	1933	125	125	2-4 years	35	25	14	11	40
Trojan	1933	33	33	1-1½ years	5	13		2	13
Charrier	1933	26	24	3 years	4	6			14
McIndoe	1934	42	42		18				6†
Perera	1934	14	14		10	4			
Ostrowski	1934	26	25		6	12	4	3	
Neddermeyer	1934	16	?			7			
Head	1934	28	28		10	15	2	1	
Coryllos	1935	20	20		5	7	6		2
Raznowski	1935	10	9	2-3 years	2		5	2	
Scholz	1935	16		3-5 years	10				
Tallyal Roth	1936	23	23	7 years	14			9	
Backer Grondahl	1936	30	30	4 years	20		7		3
Beltz	1937	66	61	3½-7½ years	23		13		25

* May be the same series

† Szeloczy reported in 1933 that early good results in the Winternitz cases was 76% which diminished to 20% after three years

‡ Steele 1937 reported same series with 46 more cases Claimed 85% cavities closed where operation was technically successful.

Plombe have been used. Steele reported five cases performed at Alexander's Clinic. Behrens has reported three cases. Jehn reported a cure in one case. Cetrangolo and Huber have each reported single cases.

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Stocklin	1921	13	13			5	5	1	2
Ranzi	1922	10	10			4	2		4
Brunner	1924	10	10		1	5			4
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not only used fat transplants to fill the space which he created at the time of performing a thoracoplasty, but also used pieces of rib as a Plombe. The pectoralis flaps of de Winter were used in conjunction with a wide rib resection.

Steenstrup recommended apicolysis with fat implantation as an adjunct to thoracoplasty. Bruns and Casper, in 1932, reported 12 very successful results with the following procedure which took the name of "Caspar Operation." Large rib resections of the first five to seven ribs were performed, preserving the periosteum. An extrapleural pneumonolysis was then performed over the exposed lung with severance of the intercostal muscles. The cavity thus formed was packed with 20 per cent argyrol gauze, the pressure being exerted from behind forward, and not from above downward. Gauze tamponades were used until a new-formed osseous bridge produced a solid barrier against which the lung could no longer reexpand. Bernou, Berard, and Proust all recommended the conjunction of an apicolysis with partial upper selective thoracoplasty. Berard did not feel that the removal of the transverse processes was necessary but Proust, on the other hand, felt that this was important in order to obtain a good collapse.

Holst, in 1932, advocated the following procedure after resection of the second rib, a wide extrapleural pneumonolysis extending below the level of the cavity was performed. The remaining upper four to six ribs were then resected. A flap was then formed from the soft parts, including muscle and periosteum. This was placed over the apex of the collapsed lung and held in place by means of packing. This packing was removed in five to seven days and a drain inserted. Although there was a severe postoperative reaction, due to suppuration in the wound, five cavities out of seven were closed.

Nissen combined apicolysis with upper partial thoracoplasty where the cavity was adherent to the apex and the vertebrae. The anterior lateral thoracoplasty, practiced by a number of Italian surgeons, combined the use of phrenicectomy and scalenotomy in one stage, resection of large pieces of the fourth to the eighth ribs in the axillary line at a second stage, and resection of the third, second and first, together with apicolysis, at the third stage. Thompson, in 1934, advocated the extrapleural stripping of the lung after upper rib re-

section in order to prevent the cavity from remaining suspended at its apex. He believed that it was necessary to remove all the fixed points of adhesions so as to allow relaxation towards the hilum.

Lilienthal has been a staunch advocate of the use of apicolysis combined with upper rib resection. In fact, he has found it unnecessary on occasions to remove the first rib in the presence of an extensive freeing of the apex of the lung.

Szeloczey has used an apical rib resection, plus apicolysis, to collapse an adherent apical cavity in the presence of a good pneumothorax over the lower lobe. He also performs an extrapleural pneumonolysis during revision operations for unsuccessful thoracoplasties by stripping the lung away from the vertebrae and inserting a bundle of intercostal muscles.

Kinsella, in doing revision operations, does not separate in the extrapleural plane because of the danger of perforating the lung, but places packings upon the muscles and periosteum and then presses the scapula over the packings. He uses gauze soaked in 1-1000 acriflavine with tube drainage at the top and bottom of the wound. This packing is allowed to remain in place for as long as 48 days. The new formed bone and fibrosis prevent reexpansion. In 13 cases in which this revision operation was performed, 11 cavities were closed and a negative sputum was obtained in all 13.

Neuhof suggested the use of a procedure which he named "Pneumocavernolysis." After a moderate posterior rib resection of the upper four to five ribs, the lung is stripped from the chest wall anteriorly and over the apex. If the lung is enclosed in a thick, calcified pleural sheath, this is carefully pared away until only pulmonary tissue remains. Packing is then inserted over the collapsed lung and kept in place as a tamponade for a number of weeks. Neuhof reported good results in a series of 34 cases.

In the last few years, the most popular type of pneumonolysis to be combined with selective partial thoracoplasty has been the type advocated by Semb. This is not an extrapleural pneumonolysis in the true sense of the word. It is, on the other hand, as Semb designates it, an extrafascial apicolysis. It is performed external to the endothoracic fascia and periosteum so that when it is completed, the periosteum remains attached to the lung and forms a new bridge of

osseous tissue on the collapsed lung. This technique of Semb has found wide approval amongst thoracic surgeons throughout the entire world. It has proven to be the best procedure for the collapse of the apical cavity which is adherent to the brachial plexus, the subclavian vein and the vertebral column.

EXTRAPLEURAL PNEUMOTHORAX

Extrapleural pneumothorax was first mentioned by Tuffier in 1891, when he described his original extrapleural pneumonolysis which he performed at that time without the insertion of any extraneous material. Both in 1910 and in 1914, he offered the procedure as a definite method for the treatment of tuberculosis. Mayer, in 1913, described a procedure in which he created a partial extrapleural space. The lung remained collapsed for three or four weeks and then, when reexpansion began he filled the extrapleural cavity with air.

Mayer also performed an apical extrapleural pneumonolysis over the site of an adherent cavity when there was an incomplete intrapleural pneumothorax over the lower lobe. By opening the pleura through the extrapleural space, he converted the intrapleural and extrapleural cavities into one and even went so far as to cut adhesions through this opening. Jessen, who was the most persistent user of various types of extrapleural pneumonolyses, used an open extrapleural pneumothorax. After the lung had been collapsed, he did not close the soft tissues but allowed the wound to remain open so that the extrapulmonary pressure was the same as that within the trachea.

Eden, in 1918, performed a pneumonolysis over the upper lobe with the intention of inserting air into the extrapleural space and maintaining a pneumothorax in that way. Unfortunately, perforation of the cavity occurred, the dead space was then obliterated by thoracoplasty but the patient died. Postmortem examination showed a collapsed lobe with fibrosis of the cavity, and Eden came to the conclusion that pneumonolysis was sufficient to cause healing and might be of value as a procedure to be performed prior to thoracoplasty.

Rieckenberg, in 1920, performed a manual pneumonolysis upon two patients, but from the description one cannot tell whether it was extrapleural or intrapleural. In both cases, air was injected under low pressure and pneumothorax maintained for some time. Follow-up

results were not given. Ulrici, through an incision parallel to the seventh intercostal space, freed the entire lung from the diaphragm to the apex by blunt dissection, leaving the diaphragmatic pleura in situ. After careful closure of the wound, by suturing the ribs together, he attempted to maintain a pneumothorax but was unsuccessful because of reexpansion of the lung and the development of infection. Riviere and Romanis, in 1923, described two cases in which the lung was separated extrapleurally without removal of a rib segment. In one, they waited twelve days before giving air and then found that the lung had reexpanded. The second case had air injected earlier but the patient died in seven weeks because of suppuration in the extrapleural space.

Harald Jessen, in 1927, reported on nine cases of extrapleural pneumothorax. Of these nine, one was cured over a period of ten years, two had been temporarily improved, one living three years and the other five years, both then dying from progression on the other side. In two cases, the outcome was unknown. Four had died, two from progression of the disease and two from hemorrhage.

Frangenheim, in 1930, found that the lung tended to reexpand after simple apicolysis and suggested that the injection of either air or oil could be used to prevent this reexpansion. Toussaint described an extrapleural oleo pneumothorax in which the wound was packed for two days with a paraffin eucalyptol gauze and then a paraffin oil mixture injected. Krampf also used the method of combining an extrapleural pneumothorax with an intrapleural collection of air by freeing an adherent apical cavity in the extrapleural plane and then opening into the intrapleural space. He maintained this combined pneumothorax and later found that the opening into the intrapleural space closed, permitting him to institute an extrapleural oleothorax. Sebestyen, using a procedure somewhat similar to Mayer, performed an extrapleural pneumonolysis where an incomplete pneumothorax was complicated by blunt apical adhesions. He carried his pneumonolysis down to the area of the intrapleural pneumothorax, opened the pleura and incised around the blunt adhesions. When these were freed, the lung collapsed. He then had a combined intra and extrapleural pneumothorax which could be maintained as long as a year. In twelve cases, he had seven cures. Most of these pneumothoraces had to be converted into oleothoraces.

Nissen, in 1931, reported the use of extrapleural pneumothorax in

five cases. Three died of progression of their disease. Two were followed with satisfactory results. Zandonini used a 5 per cent gomenol paraffin mixture in the extrapleural space following pneumonolysis. Jachia performed an extrapleural pneumonolysis in two cases and injected a mixture of lipiodol and the patient's blood. This caused a reaction with an effusion which compressed the lung for a short time. The wall of the newly formed space became fibrotic and the space was filled with air. Romanis and Sellors also tried injection of gas into the extrapleural space but found it was rapidly absorbed from the raw surfaces and surgical emphysema was a very common sequel.

It is evident that up to 1936, all the attempts at the creation and maintenance of an extrapleural pneumothorax were performed sporadically, and apparently no one was sufficiently satisfied with the procedure to persist in its use and to try it on a large series of cases. In 1936, Graf suggested that the procedure could be standardized and, if used in the correct type of patient, would undoubtedly be of value in the treatment of pulmonary tuberculosis.

After the pneumothorax has been maintained for a short time, there is frequently a tendency for the lung to start to reexpand. In these cases, the pneumothorax is converted into an oleothorax in the same manner as it is done intrapleurally. This is necessary in a large percentage of cases, especially those which are complicated by effusions, either sterile, tuberculous or secondarily infected. Schmidt and Adelberger also made a preliminary report on this method in 1936.

In 1937, Graf reported that he had performed extrapleural pneumothorax on 107 patients, with 7 deaths all occurring in the first 40 cases. No results were given because he felt that the follow-up period was too short. Hautefeuille and Dreyfus, in France, also became enthusiastic. Rhodes in England, described the procedure and Roberts reported on 33 cases. Of three very sick patients, two died and one was improved. Of 30 bilateral lesions, but with the possibility of cure, 25 were clinically doing well. In 18, the cavity had disappeared.

Coryllos has reported on 12 cases in which there were practically no technical difficulties but the follow-up only covered a period of a few months. Mutschler, because of inability to maintain the extra-

pleural pneumothorax, inserts an olive oil preparation at the time of operation. He fills one third of the cavity with the oil and allows the serous exudate to fill the remainder.

Schmidt, in 1938, reported on 200 cases of whom 25 had died. Of the surviving 175, 121 have negative sputum. The cavity is not visible in 93. The technique of the procedure is similar to that for any extrapleural pneumonolysis except that Graf and Schmidt strip the lung over a much wider area than had previously been attempted. The lysis is carried as low as the seventh rib posteriorly in practically all cases. A minute description of the procedure has been published by Graf. The postoperative care is extremely important. Occasionally, air must be injected on the night of operation and daily thereafter for a number of fillings. Fluoroscopy must be done daily. The pressure should never be increased over plus 10 and if higher pressures are necessary, oleothorax should be begun.

Bellinger has reported the use of the "Tomograph" for postoperative x rays. He feels that with the use of this device, a more exact picture can be obtained as to the postoperative result and the status of the cavity.

The complications are itemized by Schmidt and although occurring frequently, may be handled to a successful conclusion. Early mortality was four and late mortality was 21. In 20 cases, there was a hemorrhage into the space but in five of these, pneumothorax could be maintained and in eight oleothorax was instituted. Only 45 cases had a dry space postoperatively. Of these, 25 were continued as pneumothoraces and 14 as oleothoraces. In 72 cases an aseptic exudate occurred. Nineteen of these were carried over into pneumothoraces and 41 into oleothoraces. Nineteen developed sterile pus, of which 13 were converted into oleothoraces by means of gomenol. There were 8 tuberculous exudates, two of which were converted into oleothorax and three are still being aspirated. There were 31 secondary infections, five non toxic and 26 toxic. In the non toxic group, four have oleothorax. In the toxic group, 8 have oleothorax, four are being aspirated and six have been drained. Of the deaths, six occurred in the dry cases, and six in the aseptic exudate group. One case with sterile pus died, and three cases with tuberculous suppuration ceased. Of the 31 secondarily infected, nine died.

From these statistics of Schmidt, covering a series of 200 cases, we can see that there are numerous complications which have to be dealt with postoperatively and unless the end results warrant it, this procedure will not attain a definite place in the surgical therapy of pulmonary tuberculosis.

Emmler and Roberts have each recently reported a case of bilateral extrapleural pneumothorax.

SUMMARY

It is evident from the history of the use of extrapleural pneumonolysis in the therapy of pulmonary tuberculosis that the procedure is one which has little to offer as an independent measure. Up to the present, this has applied to all the modifications which have been attempted. Whether extrapleural pneumothorax with its lately revised technique will have greater success is still to be seen.

When the surgeon is called upon to treat bilateral pulmonary tuberculosis, the probability of success is immediately diminished because of the nature of the disease itself.

When one surveys the complications which may occur with extrapleural pneumothorax, and knowing how poorly the patient with extensive tuberculosis withstands any complication, it is apparent that there must be many failures.

If the percentage of good results is sufficiently high, any surgical procedure will automatically become widely used. If, on the other hand, the good results are few in number, the question arises as to the usefulness of the operation. Granting that bilateral pulmonary tuberculosis has a very poor prognosis, is it warranted to operate upon a large number of patients in order to save a few, bearing in mind that the lives of the others will be shortened or made less happy? This is a question which every surgeon must decide for himself or in conjunction with the patient.

Extrapleural pneumonolysis, as an independent procedure, will find its usefulness in the exceptional case of pulmonary tuberculosis, probably the patient with unilateral apical disease in whom thoracoplasty is contraindicated because of age or extra-pulmonary pathology.

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¹ Abstracted in Zentralblatt für die gesamte Tuberkulose forschung

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THE DECREASE IN FUNCTIONAL CAPACITY OF THE LUNGS AND HEART RESULTING FROM DEFORMITIES OF THE CHEST PULMONOCARDIAC FAILURE

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From the Medical and Cardiac Clinics of the Massachusetts General Hospital and the Fatigue Laboratory of Harvard University

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I INTRODUCTION

Those afflicted with severe chest deformities are greatly handicapped and rarely live to old age. Such deformities have occasionally proved fatal through secondary effects such as pulmonary infection, paraplegia or esophageal obstruction, but the most dramatic and probably the most frequent cause of death of the hunch backed has been pulmonocardiac failure. Heretofore little attention has been given in the English medical literature to this bizarre syndrome. In 1921 Finley in Canada remarked on the "almost complete absence" in English medical literature of any reference to the effects of scoliosis

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I INTRODUCTION

Those afflicted with severe chest deformities are greatly handicapped and rarely live to old age. Such deformities have occasionally proved fatal through secondary effects such as pulmonary infection, paraplegia or esophageal obstruction, but the most dramatic and probably the most frequent cause of death of the hunch backed has been pulmonocardiac failure. Heretofore little attention has been given in the English medical literature to this bizarre syndrome. In 1921 Finley in Canada remarked on the "almost complete absence" in English medical literature of any reference to the effects of scoliosis

thoracic viscera and he then presented 4 such cases dying with signs of heart failure. The first report in England (18) appeared under the title, "fatal cardiac failure occurring in persons with deformity of the chest." In the United States a single such case was reported by Reid in 1933. Later Carr described the cardiac changes in two cases of funnel chest and recently Truesdale and Pratt reviewed the previous surgical efforts made to relieve this deformity and described their modification of the operative technique in helping one patient.

In sharp contrast to this we find numerous clinical notes on "scoliotic heart disease" in the French and German medical literature. Comments have also appeared in Italy (39), Russia (40) and the Argentine (13). Knowledge of this ailment had become so well established in France by 1883 that Constantin Paul included in his text on heart disease an entire chapter entitled "Le Coeur de Bossus." Romberg warns in his text book that high grade kyphoscoliosis almost always die in heart failure and he mentions that Curschack had observed this 26 times in the Leipzig clinic.

Although the syndrome of pulmonocardiac failure is rare in that it is confined to those with severe chest deformities, we believe that it is of frequent occurrence in those deformed. The succession of changes in the lungs and hearts in these patients follows a recognizable clinical pattern.

The present report is a contribution toward the better understanding of this syndrome of pulmonocardiac failure in individuals with chest deformities. It includes an historical review of the subject, clinical and some pathological observations on twelve patients with severe kyphoscoliosis and finally the results of critical studies designed to estimate and explain the decrease in the functional capacity of the lungs and hearts of those afflicted.

II HISTORICAL REVIEW AND SUMMARY

Although the earliest recognition of the rôle of pulmonocardiac failure in chest deformities is obscure, the 46'th aphorism of Hippocrates (1) may be quoted, "Such persons as become hump-backed from kyphosis or cough before puberty die." Undoubtedly Hippocrates and physicians of later centuries observed the truth of this terse statement as it is well known that such persons who acquire severe

chest deformity in youth die at an early age. Although these physicians recognized the dyspnea and untimely death of the hunch-backed one gains the impression that they (20, 47) attributed the effects entirely to compression of the lungs as little or no mention is made of the possible effects on the heart and circulation.

A review of the literature concerning the effects of chest deformities on thoracic viscera enables us to present the following summary.

The incidence of chest deformities is unquestionably high but no accurate figure is available nor can we estimate the number of those who suffer pulmonocardiac failure. From all sources that appear in the bibliography we found 126 reported fatal cases. Obviously this material can not be treated in a strictly statistical manner as essential points were frequently omitted in the individual reports.

The etiology of these deformities is not always clear. Although poliomyelitis was unrecognized as such at the time of earlier reports, it is possible that it has always been the chief cause of thoracic deformities. Congenital or hereditary defects, rickets, and finally tuberculosis have been the other etiologic factors in their probable order of occurrence.

Deformities of the thorax are usually classified as lordosis, kyphosis, scoliosis, kyphoscoliosis, pectus excavatum (funnel chest) and pectus carinatum. It is doubtful if moderate kyphosis, scoliosis or pectus carinatum ever cause harmful intrathoracic changes. However it is plain that severe kyphosis or scoliosis, either of which usually becomes kyphoscoliosis, and the funnel chest often cause changes in the thoracic viscera sufficient to produce the symptoms and signs of pulmonocardiac failure. Neidert (4) concluded that with severe spinal curvature death came through heart failure, lesser grades disposed to tuberculosis while mild or slight deformities had little or no influence on life expectancy. Fixation of the spine and ribs in spondylitis and artificial pneumothorax are known (35) to reduce the vital capacity but pulmonocardiac failure has never been recognized as a complication.

Severe chest deformity occurs in both sexes but more often in the male. For some unaccountable reason the incidence of right sided kyphoscoliosis is far greater than left, in only 15 of the 126 cases was it stated that the curvature was toward the left side. In a right

sided deformity the primary curve in the dorsal vertebrae is directed to the right of the mid line. This produces a bulging or convexity of the right chest wall while the secondary or compensatory curve bends the vertebral column sharply to the left causing a compression or concavity of the left chest. This is an important observation as it has led to the theory that pulmonocardiac failure in right sided deformity is due to compression of the left chest which in turn oppresses the heart and forces it over against the left chest wall.

The outstanding symptoms of the embarrassed lungs and heart in their order of frequency are dyspnea, palpitation, cough and epistaxis. Precordial pain was noted only twice. Most of the patients acquire the angulation of their spines in youth and the deformity increases until about the age of 18 or 20 years. Symptoms usually appear within a few years after the deformity reaches its maximum. Once severe symptoms develop the interval before death is usually short.

The average duration of pulmonocardiac failure in 18 cases was 5 months although in 10 others symptoms had been present many years. The average age at death of 79 patients was 30 years. The rapid development of pulmonocardiac failure, with congestion and edema as terminal manifestations, gives little advance warning to the physician.

Dyspnea is the chief symptom in these patients. Schneevogt in 1854 was the first to measure accurately the diminution in their vital capacity which he did by means of the spirometer. Another important observation on the breathing of those with chest deformities has been made by de Vesian who pointed out that they have a normal or habitual dyspnea. Because of changes in the thoracic cage they breathe with effort, often using the ribs inefficiently. Abdominal muscles then play a large rôle and the respiration becomes chiefly abdominal in type. This habitual dyspnea increases in these patients until they notice that slight exertion troubles them and soon they become subject to attacks of paroxysmal dyspnea, asthma or even episodes of great weakness and fainting. This transition from habitual dyspnea to severe symptoms marks the onset of pulmonocardiac failure.

The outstanding signs of pulmonocardiac failure are dyspnea and a

persistently rapid heart rate Irregularity of rhythm has been noted only by de Sottas and Boas Hypertension was thought by Dumas to be significant but usually there is little if any increase in the systolic pressure but often an increase in the diastolic level Edema of the legs, usually a terminal sign, is not common and anasarca is rarely observed Characteristic heart murmurs have not been described although the second pulmonic sound is often accentuated and in a few a systolic murmur is heard Enlargement of the heart is obviously difficult to detect when changes in the conformation of the chest occur but displacement toward the right and upward is usual Fluoroscopic observations by Rosler and Edeiken in cases of kyphoscoliosis revealed a "mitral shaped heart" with evidence of right sided enlargement in most instances It is their opinion that these changes occur only with right sided kyphoscoliosis as in left sided deformity the heart lay more in the median position and its appearance was little altered

The morbid anatomy has been adequately described in 69 of the fatal cases discovered in the literature

In regard to the heart, 45 of the 69 had hypertrophy and dilatation of the right ventricle, in 2 cases there was dilatation of the right auricle alone One case is described as having dilatation of the right ventricle and pulmonary artery, in another with a large right ventricle the pulmonary artery was small In the remaining 20 of these 69 the size of the heart was considered normal or there was some slight degree of left ventricular enlargement. Ljundahl has looked for pathologic changes in the pulmonary arteries and veins of three cases of scoliosis but he found nothing to explain the enlargement of the right heart One of his cases should be excluded as the patient had silicosis, which is known to produce an enlarged right heart (15)

In the opinion of Poissonner, atrophy of heart muscle is more common than hypertrophy although the characteristic lesion is dilatation of the right ventricle It has been suggested that cramping and spacial limitation may prevent diastolic filling of the coronary arteries in these hearts, but we found no description of significant changes in these vessels and there has been no recorded electrocardiographic evidence of coronary vessel disease The exhaustive study in the pathology of the cardio-vascular systems in 276 cases of chest de-

formities by Bachmann is somewhat confusing when one considers that 36 of his cases had valvular heart disease, 70 had some pericardial changes and 129 had degenerative myocardial disease

Congenital cardiac defects have been described (9, 16) as additional burdens in two patients

The morbid anatomy of the lungs has been extensively studied and yet there is no agreement as to the effect of thoracic deformity on the lung tissue Rieder was impressed with the actual disappearance of lung substance following a partial collapse Both Rieder and de Gouraud found compression in some areas and compensatory emphysema in others In contrast to this May, who studied two cases in frozen sections, was impressed with the total decrease in the size of the lungs rather than a change in shape or microscopic appearance Atrophy of the lung seemed apparent to de Vesian and in one of his cases the total lung weight was only 590 gms The tendency of the collapsed lung areas to harbor infection or to fail to resolve after pneumonia has been stressed by Bertsch

Bachmann gives perhaps the best evidence of pulmonary changes as he states that in his 276 cases of thoracic deformity there was pneumonia in 60 per cent, emphysema in 46 per cent, bronchitis in 41.6 per cent, atelectasis in 31.2 per cent and bronchiectasis in 6.1 per cent

In the past the explanations for this syndrome of pulmonocardiac failure have not been adequate to explain all the foregoing clinical and pathological manifestations On the basis of a single case in which the aorta was sharply angulated along the spine Corvisart postulated that aortic obstruction is the common cause of these symptoms However, examination of the heart in his case, as in Klavansky's, revealed right and not left sided cardiac hypertrophy that one would expect with aortic obstruction As early as 1828 Delpech called attention to the displacement of the heart and great vessels in gibbosity Although the myocardium in these cases may have suffered poor nourishment and anoxemia there has been no direct evidence to support Meyer's (36) theory of cardiac compression Dedic observed by fluoroscopy that the diaphragms in his cases were elevated and because of their position and poor excursion he believed that the return of blood to the right heart was impeded Forget,

de Sottas and Barie have interpreted the terminal process as one of heart failure alone, but they presented no conclusive evidence or reasoning for such an assumption

De Vesian in 1884 was possibly the first to place emphasis on the part played by failure of both the lungs and heart in those with chest deformities. He pointed out that diminution in lung volume and dilatation of the right ventricle are consecutive to chest deformities, and that these patients ordinarily die after a series of attacks of asystole or in asphyxia as a result of acute pulmonary infection which further decreases the vital capacity. His interpretation of the primary effect being on lung tissue and the consequent embarrassment of the heart seems to us a most reasonable explanation but it still leaves us uncertain of the exact mechanism of pulmonocardiac failure.

The treatment of pulmonocardiac failure has been balked largely by the very nature of its cause. Usually the deformity reaches its maximum by the 18th or 20th year. Before this age spinal fusion has been done to arrest the deformity but the results appear to have been only partially successful, after this age the patients usually wear braces and supporting jackets with some relief. Brugsch exhorted the orthopedic surgeons to exercise great caution in undertaking any surgical procedures on these patients because of their tendency to develop alarming pulmonocardiac symptoms. Actual surgery of the chest for relief of the effects of funnel chest was first tried in 1911 by Meyer (37) and since then the reports of Sauerbruch, Carr and Truesdale have been encouraging.

Treatment of the cardiac failure itself has followed the usual lines with rest, diuretics, bleeding and digitalis. These measures have been of little value in relieving the progressive symptoms and signs of pulmonocardiac failure. The use of morphia in these cases has been condemned by Schroeder for its respiratory depressant effect. As a measure for the relief of acute symptoms de Vesian advised the inhalation of oxygen as early as 1884. General hygienic measures and a particular effort to avoid respiratory tract infection are of paramount importance in these individuals. As mentioned before, pulmonary infection in the compressed lung often leads to grave symptoms and may precipitate a rapid pulmonocardiac failure.

III CLINICAL INVESTIGATIONS

The previous paragraphs have summarized the recorded facts concerning pulmonocardiac failure caused by structural changes in the thoracic cage. Here in Table I are summarized the chief points of clinical interest in twelve additional cases. Of these twelve, four died in pulmonocardiac failure, six are living a very restricted life and the remaining two are little handicapped. One of these cases is of particular interest as it was possible to contrast him with his normal twin brother.

From table 1 and the clinical histories appended it is clear that the general pattern of this disease follows that previously described and need not be repeated here. It is necessary, however, to add a few new observations and to emphasize certain details already mentioned.

An important and little mentioned fact is that the deformity in these people has so hindered their general development that their appearance suggests dwarfism. They are small, shy, poorly nourished and frail-appearing. It is somewhat surprising that clubbing of the fingers was universally absent. Unfortunately their tendency to complain has been frequently interpreted as a psychoneurotic manifestation. This was true in three instances of the present series and one of these was receiving psychotherapy until a short time before his death.

Ten of the twelve had a right sided kyphoscoliosis and two had a left sided deformity. The deformity in ten cases had gradually increased from early age until adolescence at which time it became relatively fixed. In one case, W. C., the deformity developed after adolescence. The study of this individual offers surprising data, the possible significance of which will be discussed later. The shortest duration of the deformity was seven years and the longest forty-four years before pulmonocardiac symptoms appeared. Five of the twelve declared that they obtained relief of symptoms in the recumbent position, some even attempting hyperextension of the spine for relief, this has been a hitherto unmentioned feature. Sudden fainting attacks, during which the patients lose consciousness and become momentarily pulseless and cyanotic, are probably similar to the episodes of asystole so often mentioned by French physicians, these attacks may occur in the absence of the usual signs of heart failure.

Such attacks occurred in three of the twelve and were observed, with considerable alarm, in two. From the observations of the critical episode in Case I and the fatal outcome in Case 4 Schroeder is confirmed in his opinion that morphine or other respiratory depressants should be used with great caution.

Habitual dyspnea was admitted by all but one of the twelve and he was one of the two with a left sided deformity. Just when the habitual dyspnea becomes severe enough to mark the onset of pulmonocardiac failure is as yet a matter of individual clinical opinion.

In the review of the literature concerning the effects of chest deformity there was no mention of investigations designed to measure the functional capacity of the lungs and hearts of the patients. This very problem was undertaken with the hope of explaining better the physiological sequence of events which leads to untimely death in pulmonocardiac failure. Although the results of this study have not revealed a complete explanation we offer here the data obtained with limited interpretations.

Methods of investigation

First, measurements of body size and weight were made and the DuBois formula was applied to estimate the body surface area.

Second, the lung volume and its subdivisions were determined. The method of Christie was used in determining residual air, in these measurements the only values discarded were some of the first and a few subsequent ones in which too little oxygen had been used.

The third step was studying the respiratory metabolism by measuring the carbon dioxide production, respiratory volume, basal metabolism and then the response to breathing a mixture containing a low partial pressure of oxygen. To test this response a mixture containing 12 ± 0.2 per cent oxygen was prepared and the subjects inspired this through the same mouthpiece and valve used for the metabolism determinations. They were under the impression that the same sort of test was being done and in all but two cases no discomfort was experienced. Samples of arterial blood were drawn before and after the subject had been breathing the mixture for several minutes and also while he continued to breathe it.

Fourth, observations on the circulation included the cardiac output

	Died April 1935 Crisis precipitated by respiratory depression
	Died May 1932. Diagnosed cardiac neurosis
	Died March 1933. Treated with psychotherapy Autopsy record
	Died March 1936. Respiratory failure from morphine
	Living limited to house. Diagonal anxiety neurosis noted
	Living with limited activity Relieved in recumbency
	Living, very limited. Asthma and fainting attacks
	Living activity only slightly limited
	Living activity only slightly limited
	Living, active
	Living, very limited. Relieved in recumbency
	Living, inactive but denies symptoms

* This patient also had a funnel chest.

† Familial

determined by Grollman's acetylene method and direct venous pressure readings. The circulation time from arm to tongue, using the method of Winternitz as modified by Gargill, was done in 3 cases. The early trials in measuring cardiac output were unsuccessful because proper allowance had not been made for the low vital capacity of these subjects. By suitably reducing the volume of the mixture, lengthening the preliminary mixing period to 12 seconds and continuing the rebreathing period to 25 seconds satisfactory duplicates were obtained.

Finally the properties of arterial blood were determined under normal conditions. The methods used here and for the estimation of partial pressure of carbon dioxide in the blood and alveolar air were the same as those previously described in reports from the Harvard Fatigue Laboratory.

Results of investigation

Body measurements and values for the several divisions of the lung volume of these patients are given in tables 2 and 3. The measure of the effects of the disease on the height and weight supports our previously mentioned clinical impression that general development is retarded by spinal curvature. This is best seen by comparing W D with his normal, identical twin brother, J D. The height of W D is 12 per cent, the weight 39 per cent and the surface area 26 per cent less than that of his normal brother. The oxygen consumption in both was similar when considered in relation to the surface area.

Figure 1 shows the subdivisions of lung volume that were measured. One of the striking features in the measurements of lung volume was the absolute and relative reduction in vital capacity. The values for the vital capacity ranged from 700 to 2520 cc which represents a decrease to about one half the normal value. Furthermore, the vital capacity constitutes from 35 to 53 per cent of the total lung volume in these patients while in the normals studied it amounted to 57 to 69 per cent of the total. The averages are 44 and 63, respectively. It is to be noted, however, that in the patient W C the residual air is considerably higher than all others and comprises 58 per cent of the lung volume. This suggests the presence of a true emphysema. The ratio of residual air to vital capacity is 1.3 in the patients and 0.6

in the normal subjects, this best explains the respiratory difficulties and habitual dyspnea that these patients suffer. The mean deviation between the final duplicate values for residual air in patients was 180 cc with only one value greater than 210. From 4 to 6 consecutive determinations on each of 5 normal subjects yielded more concordant values, the mean deviation was 110 cc.

TABLE 2
Body measurements

	I P	A P	L S	R B	W C	W D	J D	M N
Sex	Female	Female	Male	Male	Male	Male	Male	Male
Age	22	45	17	17	38	31	31	24
Height, cm	138	146	169	175	165	152	173	138
Weight, kg	33.3	37.1	56.0	50.8	59.6	45.5	74.4	33.3
Surface, m ²	1.12	1.24	1.64	1.60	1.64	1.4	1.89	1.12

TABLE 3
The lung volume and its subdivisions
Measurements in cubic centimeters

	HYPOSCOLIOTICS						NORMALS					
	I P	A P	L S	R B	W C	W D	J D	O D	DD JR.	D D	A L	B D
Vital capacity	700	1460	1330	2230	2620	1220	4050	2720	4180	4500	5200	3190
Complemental air	420	990	800	1430	2100	950	2350	1655	3240	3580	3610	1990
Supplemental air	280	470	530	800	420	270	1700	1065	940	920	1590	1200
Tidal air	160	320	375	430	390	400	490	360	520	435	430	480
Residual air	1300	1720	1295	1955	3530	1115	2505	2040	2310	2930	2780	1450
Per cent in total volume of												
Vital capacity	35	46	51	53	42	52	62	57	64	61	65	69
Residual air	65	54	49	47	58	48	38	43	36	39	35	31

* Twin brothers.

Table 4 shows that the average basal metabolic rate of seven of the twelve patients is plus 5, while the number of cases is too small to yield a reliable average it is likely that the average metabolism is lower as the Du Bois formula probably gives too small a surface area for persons with structural deformities. The irregular contour in-

creases the surface area over that of the normal person of corresponding height. The respiratory volume tends to be larger than that of the normal person having the same oxygen consumption. This is shown by dividing the respiratory volume by the oxygen consumption, those with kyphoscoliosis breathe from 25 to 35 liters of air for each liter of oxygen absorbed while J D (normal) used only 22. Expressed in another form, the amount of oxygen abstracted from inspired air is usually from 4 to 5 per cent, while in our series the

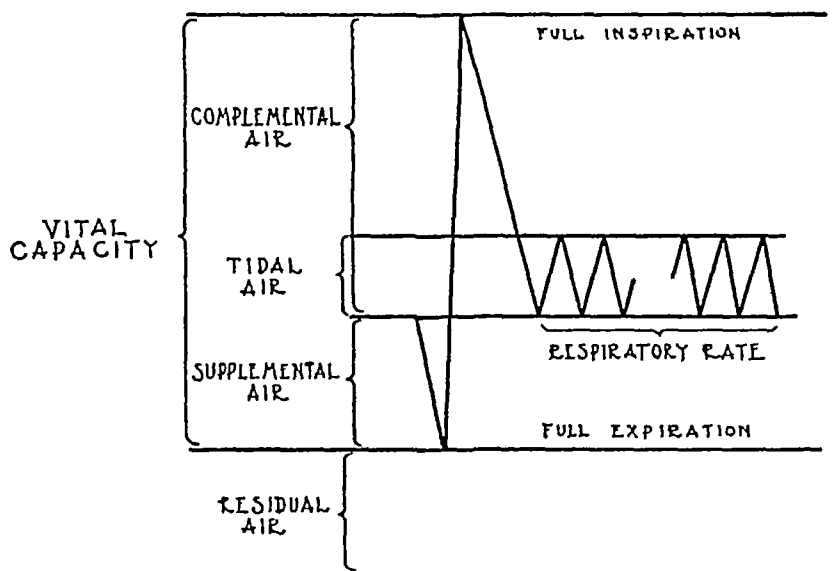


FIG 1 NORMAL RESPIRATORY VOLUMES

amount was only 3.45. The reason for this is probably the relatively small amount of residual and supplemental air.

In testing the response to low oxygen pressure, patient M N caused considerable alarm by having an attack of acute, non-fatal pulmonocardiac failure. After breathing 12 per cent oxygen for a few minutes she became cyanotic, pulseless and comatose while lying flat. Recovery took place slowly and she was able to walk with aid at the end of an hour. Further studies were not attempted. The second patient, I P, had a similar attack about one half hour after the tests were completed. Both of these subjects, as well as W C, the third person liable to such attacks, show evidence of pulmonary

TABLE 4
The respiratory metabolism

	I. P.	A. P.	M. N.	L. S.	R. B.	W. C.	W. D.	J. D.
Oxygen used, L./min	0 160	0 176	0 180	0 251	0 208	0 217	0 186	0 262
CO ₂ produced, L./min	0 126	0 143	0 149	0 219	0 186	0 201	0 162	0 215
R.Q.	0 79	0 80	0 83	0 78	0 89	0 93	0 87	0 82
B.M.R.	+6	+15	+19	+14	-12	-2	-2	+1
Respiratory rate	24	22		16	18	15	15	11
Resp. vol., L./min	4 22	5 67	4 55	6 97	6 30	7 54	4 56	5 66
Resp. vol., L/O ₂ used	26	32	25	28	30	35	24	22

Response to low oxygen (12 ± 0.2 per cent) for 5 to 15 minutes								
Respiratory rate	20	25	17	18	18	14	14	14
Resp. vol., L./min	4 60	8 70	5 70	9 50	7 18	7 61	6 12	6 42
Resp. vol., per cent inc	9	53	25	36	14	1	34	13
Pulse	88	102	104	76	133	88		78
Δ pulse	4	18	12	12	7	2		10
HBO ₂ cap, vols per cent	14 63	†	†	14 40	19 60	19 09	18 90	18 50
HBO ₂ content, vols, per cent	12 75			12 12	15 80	14 28	15 78	15 88
Oxygen saturation, per cent	77 6			84 0	80 6	74 9	83 5	85 8
Cell volume, per cent	42 0			35 6	44 4	41 8	42 1	40 9
Total CO ₂ , vols, per cent	49 5			52 1	45 2	52 0	52 8	50 9
H ion concentration	7 33			7 41	7 36	7 33	7 39	7 36
Art. pCO ₂ mm. Hg	45 5			41 0	39 8	47 5	42 5	42 4

† Pulse = increase in pulse rate

* Twin brothers.

† Patient uncooperative.

† Acute pulmonocardiac failure, blood not obtained

deficiency, in table 4 it is seen that they show a high arterial p CO₂ under normal conditions and a notable fall in oxygen saturation on breathing 12 per cent oxygen, which is the equivalent of attaining an altitude of 14,500 feet. The others were not distressed by breathing the low oxygen mixture. The percentage increase in ventilation was considerably greater in some cases than is observed in normal subjects, it is well here to compare the twin brothers. The increase in heart rate, however, in all instances is normal.

Table 5 shows no consistent changes in cardiac output in these patients. A P and L S have an output of about one-fifth greater than normal and R B about one fifth less than normal. Persistent tachycardia was present in six of the twelve, it was most evident in

TABLE 5
The circulation

	I P	A P	L S	R B	W C	W D	J D	J G
Pulse	84	84	64	126	86	83	68	
Arterio- venous O ₂ difference, cc	67.2	48.2	47	7.2	56	57		
Blood flow, liters per minute	2.4	3.7	5.3	2.9	3.9	3.3		
Venous pressure cms. water	8.8		3.7	6.4	3.4	7.8	9.2	7.0
Forced inspir. glottis closed	14.2		7.3	13.3	3.8	10.6		
Forced expir. glottis closed			8.4	21.0	4.4	15.5		
Circulation time in seconds (arm to tongue)			12.5	12.0				13.0

R B and may be related to his low cardiac output. There was no extreme deviations from normal in the arterio-venous oxygen difference. The venous pressures measured during rest and during forced inspiration and expiration with the glottis closed reveal no abnormalities. The circulation time from arm to tongue was normal in three instances.

The properties of arterial blood are shown in table 6. One man, L S, showed a significant anemia and it was he who had a slight increase in cardiac output, the others were on the low side of normal. The percentage saturation with oxygen was normal except in W C who had a notable anoxemia. The heightened respiratory volume, noted above, does not then cause greater than normal blood oxygenation, on the contrary, it is probably necessary if the normal gaseous

exchange is to be maintained. The blood hydrogen ion concentration, serum protein, serum chloride and base were all within normal limits.

The adequacy of gas exchange may be measured by comparing the partial pressures of arterial blood with those in alveolar air. In normal man, whether at sea level or high altitudes, equilibrium with regards to carbon dioxide is virtually complete, in three of these with kyphoscoliosis the pressure head of carbon dioxide, $p\text{ CO}_2$, is within the normal range, in the others it is slightly elevated or in other words, the difference between arterial and alveolar CO_2 is ab-

TABLE 6

Properties of arterial blood and the carbon dioxide pressure gradient in the lungs

	I P	A P	M N	L S	R B	W C	W D	J D
HBO ₂ cap, vols. per cent.	16.35	18.20	17.55	14.69	19.73	19.08	18.65	18.30
HBO ₂ content, vols. per cent.	15.51	17.45	16.42	13.71	18.81	16.71	18.17	17.60
Oxygen saturation, per cent.	95.3†	95.9	93.7	93.4	95.4	88.1†	97.5	96.2
Cell volume, per cent.	40.9	43.5	37.8	34.8	44.6	45.4	42.1	41.4
HBO ₂ cap. of cells, vol. per cent.	40.0	41.9	46.8	42.2	44.2	42.0	44.3	44.2
Total CO ₂	51.7	51.2	48.0	53.3	46.8	53.8	53.1	50.4
H ion concentration	7.36	7.35	7.38	7.42	7.34	7.39	7.34	7.36
Serum protein, per cent.	7.05	7.50	6.70	7.10	6.70	6.70	6.65	6.35
Serum chloride, me/l	102.0	103.2	101.9	104.0	104.3	103.7	104.9	101.5
Serum base, me/l	153.6	151.9		153.9	151.1	153.7	148.5	
Arterial $p\text{ CO}_2$, mm. Hg	44.9	46.0	41.6	39.9	43.0	44.5	48.5	44.2
Alveolar $p\text{ CO}_2$, mm. Hg	40.4	40.6	38.8	37.8	39.8	41.6	43.0	41.8
$\Delta p\text{ CO}_2$	4.5	5.4	2.8	2.1	3.2	3.9	5.5	2.4

Δ Difference.

* Subject to attacks of acute non fatal pulmonocardiac failure.

† One of the results from two punctures

normally great. Evidently there is no serious impairment of ability to transfer CO_2 in any of these patients and only W C was unable to maintain the normal pressure gradient of oxygen while at rest. It is possible that studies of gas exchange during muscular activity might be useful in revealing defects which are concealed in the resting state. However, because of the precarious clinical condition of these patients, we thought such studies were inadvisable. The discordant findings in the case W C suggest the desirability of comparing in a larger series the effects on the lungs of those who develop their deformity before and after the growth period.

IV SUMMARY AND INTERPRETATIONS

It seems clear that persons with severe thoracic deformities, particularly those with a right sided dorsal kyphoscoliosis, suffer an habitual dyspnea that may increase to the point of imposing a severe limitation of activity. Later on in life palpitation, fainting attacks or aggravation of the dyspnea by exertion or changes in position may harass those deformed. Such a sequence of events is sufficient to diagnose pulmonocardiac failure and to warn the physician of the precarious hold that these people have on life. The average duration of life, 30 years, may surprise some, but it has been appreciated by insurance companies for years.

The investigations recorded here are the first that attempt to explain these phenomena. In tracing the progression of events in these patients it is obvious that the primary difficulty is the thoracic deformity. Vital capacity may gradually be reduced by one half or more. As this occurs the ratio of residual air to vital capacity is doubled. Consequent to these changes the respiratory volume increases but despite this increased work less oxygen is actually removed from the inspired air. The mechanism of pulmonary exchange lacks efficiency and incomplete oxygenation of the blood may occur despite the compensatory reaction. The two patients who fainted showed this pulmonary deficiency by having a high arterial CO_2 content and a definite anoxemia produced by the equivalent of attaining an altitude of 14,500 feet. One of these was rendered comatose and pulseless by this procedure and the second developed the attack shortly after the experience.

Additional evidence that the chief effect in this syndrome is on the lungs is found in the clinical facts that pulmonary infection, respiratory depressants or any process that further reduces pulmonary function in the hunchbacked may lead to pulmonocardiac failure and even death. In those deformed, particularly after poliomyelitis, the usual mechanism of respiration is altered by the great limitation of costal movement. The ribs move only ineffectively and breathing is accomplished largely by movements of the diaphragms. Partial collapse and infection are but natural results in these poorly aerated lungs.

In general the structures within the thoracic cage, not excepting bone, give way before the spacial needs of the heart and great vessels,

as distortion of the chest progresses over a period of years there is ample time for the heart and great vessels to adapt themselves to changes in position and yet to follow the natural rate of growth, these individuals all seemed to have at least normal sized hearts

In contrast to this the lungs are soft and easily compressed. Even in normal people we know that a pressure as light as the ribs exert will mark the lung surfaces. Bremer has recently offered convincing evidence that the normal lung grows by the increase in the number of alveoli and not by their increase in size. After lobectomy he found actual regeneration of lung tissue occurring in the young while only dilatation of the alveoli occurred in the adult whose lungs had stopped growing. These important observations seem to explain the great difference of opinion mentioned before in regard to the pathologic effects of chest deformity on the lungs. It should be noted by comparing tables 1 and 3 that all of the kyphoscoliotics whose deformity started before puberty had a marked reduction in vital capacity and residual air, suggesting an underdeveloped lung. The one case, W. C., with surprisingly high values for vital capacity and residual air acquired his deformity after the growth period and so it is likely that he has a vesicular or alveolar emphysema. Atrophy of lung tissue probably does not occur, but rather the lungs can not develop to their full size in the cramped thorax, hence the frequent description at autopsy that the lungs resembled children's lungs.

We know that in many of these deformed the right ventricle of the heart is enlarged and its walls often are thickened. This is difficult to explain if we can not postulate increased work and pressure within the pulmonary circulation, unfortunately exact measurements of this kind are not feasible. We have determined that the circulation time through the lungs is normal, that the pressure in the venous system is normal, that the arterial pressure and cardiac output are usually normal, but as yet we can not measure the pressure within the right ventricle. However the tachycardia and frequent presence of an accentuated second pulmonic sound support a likely explanation that increased work and pressure are maintained by the right ventricle in order to maintain arterial oxygenation through the cramped and underdeveloped lungs. It is possible that in severe funnel chest the rotation and displacement of the mediastinum, such as Carr describes, are additive factors in pulmonocardiac failure.

Pulmonocardiac failure gradually overtakes these crippled people and as dyspnea increases we realize that the lung space has been further reduced and a greater burden has been placed on the right heart. Congestive failure of the usual type, as in our case 3, may occur or repeated crises with sudden death in a cardiac delirium, as in case 1. Still other and perhaps more frequent mechanisms are the sudden, quiet fainting attack in which the patient becomes pulseless, cyanotic and comatose, or the profound respiratory failure, as in case 4, these episodes seem to fit the descriptive French terms of terminal asystole and asphyxia.

This syndrome of pulmonocardiac failure is not analogous to the usual cor pulmonale or to Ayerza's disease. It stands alone in its peculiar manifestations.

From this analysis of the factors underlying pulmonocardiac failure it is possible to formulate rather broad concepts for its treatment. First, every effort to relieve the deformity should be pursued through the period of adolescence until the deformity is arrested. Supportive measures in the past have often been inadequate and for this reason the early use of spinal fusion operations to hold the spine in position is recommended. These are matters for the consideration of the orthopedic surgeon. The matter of breathing exercises, posture habits and a conscientious effort to correct the deformity are quite dependent on the cooperation between the patient and physician.

The tendency of these warped people to complain must be accepted with patience and it must be realized that their bizarre symptoms are not usually psychoneurotic manifestations.

When the habitual dyspnea of those deformed is replaced by the severe dyspnea of pulmonocardiac failure great personal care should be urged. Activity should be limited and mountain climbing or plane travel are to be discouraged. The prevention of respiratory tract infection is of the greatest importance and respiratory depressant drugs and anesthetics are to be used with considerable caution. In the event of actual heart failure little aid can be expected from the remedies usually employed.

We are indebted to Dr Tracy B Mallory for his aid and suggestions in preparing this paper

V TWELVE CASE HISTORIES

Case 1 F C, female, aged 29 Right kyphoscoliosis, ? poliomyelitis Fatigue, palpitation, ankle edema, dyspnea, tachycardia and cyanosis aggravated by the upright position and relieved by hyperextension Crisis precipitated by a respiratory depressant (panlopon) Sudden death in pulmonocardiac failure 2 years after onset of symptoms

An unmarried Jewish girl of 29 first entered the hospital in August, 1933. She gave a history of having a spinal curvature beginning at the age of 7 and becoming progressively worse until the age of 20. During these years she was well and worked as a salesgirl until the age of 28 when she gradually became irritable, tired easily and noted palpitation and occasional swelling of the feet.

Physical examination showed a moderately obese girl in no distress but her head was deeply set between her shoulders because of a severe, high, right dorsal kyphoscoliosis. The heart was considered normal, the blood pressure was 110 mm systolic and 76 diastolic. For the first week in bed the pulse rate varied between 80 and 100 but thereafter it remained constantly between 76 and 86.

While in the hospital she was on head traction for 16 days and was then discharged with instructions to wear a Thomas collar of leather and steel that was fitted on to a chest support. A neurological consultant found no signs of pressure on the spinal cord or nerve roots.

On January 2, 1934, she returned to the hospital complaining of shortness of breath and chest pains. She said that bed rest in hyperextension or wearing the brace relieved her symptoms and for this reason she was anxious to have the spinal fusion operation that had been suggested at the previous entry. A medical consultation was requested and she was seen by one of us (E M C) who found that she was short of breath while at rest with a respiratory rate of 30 to 40. There was no cyanosis and the heart action was rapid, 90 to 100, regular, and no murmurs were heard. The second pulmonic sound was accentuated. The blood pressure was 128 systolic and 94 diastolic. She was considered a poor operative risk because of the existence of potential heart failure due to the chest deformity. However a cardiac consultant and another medical consultant, supported by a normal electrocardiogram, declared that she was sound and so a low spinal fusion was performed under avertin anesthesia on January 16. This required 3 hours and she did well under the operation except for some cyanosis and a pulse rate that continued between 120 and 130.

Her recovery was uneventful except for continued tachycardia. February 12 she was discharged to a convalescent home where she continued to lie in a plaster shell.

On April 4, 1934, she returned to the hospital because of pain in her lower ribs and back. She was very dyspneic while sitting up but when in hyperextension with head traction she was comfortable. Tachycardia continued and her vital capacity on two trials was found to be 540 and 580 cc. A rib resection was advised and on May 4, as a preoperative measure she was given pantopon gr $\frac{1}{3}$ subcutaneously. Within a few minutes she became deeply cyanotic, extremely dyspneic and the immediate use of an oxygen tent was necessary. She continued in a critical state for the next 8 days, spending most of the time in the oxygen tent. On May 28, without preoperative medication, 3 ribs were removed from the area of greatest deformity under local and light gas-oxygen anesthesia that lasted 55 minutes. After 5 more days in the oxygen tent she emerged in fair condition and returned to her shell in hyperextension. The heart rate continued between 90 and 110. On June 12th she was allowed to go home.

On April 26, 1935, she was brought to the emergency ward because of severe dyspnea and cyanosis of 12 hours duration. She was placed in an oxygen tent with some relief. At 2 p.m. she was taken out of the tent for transportation to the ward but en route she became cyanotic, gasped for breath and her heart's pounding against the chest wall at a rate of 160 could be seen plainly. At 2:15 p.m. she received morphia gr $\frac{1}{4}$ and a venesection of 300 cc. was started. She died at 3:30 p.m. and an autopsy was not permitted.

Roentgenograms of the chest of this patient are unsatisfactory for interpretation of heart size and no fluoroscopic studies were done.

Case 2 F C, female, aged 26. Right dorsal kyphoscoliosis, Pott's disease since the age of 3 years. Intermittent attacks of sudden tachycardia and swelling of the left hand, attacks precipitated by emotion and fatigue. Diagnosed cardiac neurosis, possible paroxysmal tachycardia. Sudden death in pulmonocardiac failure 4 years after onset of symptoms.

This was an unmarried American girl who had Pott's disease at the age of 3 years and had a spinal fusion at 8 years because of an advancing scoliosis. She was seen at intervals in the orthopedic department from 1914 until 1925 and then she was sent to the outpatient medical department on March 16, 1931 because of suspected heart disease. She was then 26 years old and complained of sudden attacks of rapid heart action and si-

multaneous swelling of the left hand. These attacks had been coming about once a month for the previous 3 years. They lasted about 20 minutes and then gradually disappeared. Only in recent months had the patient noted dyspnea on exertion.

Physical examination showed a frail girl weighing 75 pounds, with a severe right dorsal kyphoscoliosis involving the upper and mid dorsal spine. She was in no distress and wore a supporting brace and jacket that had first been fitted in 1914. A few moist râles were heard in the left axilla. The heart was not enlarged to percussion, the apex impulse was forceful and a soft systolic murmur was heard at the pulmonic area. The heart rate was rapid, 100, with a sinus arrhythmia. There were no signs of congestive heart failure.

It was the impression of the medical consultant that she had either a cardiac neurosis or possibly paroxysmal tachycardia. Her family physician had told her that her heart action was rapid during the attacks. On April 6, 1931, a roentgenogram of the chest was reported as showing compression of the lower lung lobes and this was considered to be the cause of the râles. No mention was made of the heart size and since that time the films have been destroyed. She was seen again on June 12th and reported that she had had only one more attack and that was after a strenuous week end. On May 12, 1932, the patient died suddenly at home and was attended by her family physician who diagnosed it as a heart attack. An autopsy was not done.

Case 3 C S, male, aged 45. Right dorsal kyphoscoliosis, familial. Intermittent attacks of dyspnea, pain in the back, tachycardia and nervousness. Treated with psychotherapy. Asthma severe for two weeks and then death in sudden pulmonocardiac failure 1 year after onset of symptoms.

A 45-year-old American clerk entered the out patient medical department on February 17, 1933, complaining of attacks of "nervous prostration" for the previous year. The attacks consisted of periods of an hour when he had to sit up in bed to get his breath and sometimes he had to get on his hands and knees for comfort. There had been some pain in the back between the scapulae. His family physician had assured him that it was all due to nerves. The family history revealed that two brothers, an aunt and a great aunt also had lesser grades of the same type of spinal curvature. The patient's deformity had appeared in the first year of life and since the age of 15 he had lost in height from 5 feet 6 inches to 5 feet 3 inches.

Physical examination showed a surprisingly robust man who was very

anxious and restless On exertion he became dyspneic and showed a coarse tremor of the hands The examination of the heart was unsatisfactory because of his spinal curvature, but it was considered normal The blood pressure was 130 systolic and 90 diastolic The clinical impression was that he had an effort syndrome and neurosis

A review of the roentgen ray films of the chest taken on March 13 shows obvious enlargement of the right heart and although the apex reaches the left lateral chest wall the position is due to the deformity

On March 3, 1933, he seemed to feel better after a psychiatric consultation during which the psychiatrist noted dyspnea, tachycardia and a few moist râles at the lung bases On March 16th the psychiatric consultant noted "much obsessive-compulsive material about bed posture," as the patient said he had to get on his hands and knees to breathe comfortably On March 31st the patient was brought into the emergency ward because of severe asthma and for 3 nights he had been forced to remain in a chair As it was late at night the psychiatrist was not called

Physical examination now showed the man sitting on the edge of his bed puffing and wheezing The lips and nail beds were slightly cyanotic The neck veins were not engorged It was remarked that the severe right dorsal kyphoscoliosis had caused a concavity of the left chest The heart sounds were regular, 110, and the sounds were of poor quality producing a tic-tac rhythm The second pulmonic sound was loud and reduplicated The blood pressure was 140 systolic and 110 diastolic The chest was full of moist crepitations and there was pitting edema of the ankles The vessels of the retinae showed only moderate sclerosis

He was admitted to the ward in the late afternoon and received digitalis gr 3 At 8 45 p m he received morphia gr $\frac{1}{6}$ At midnight he became suddenly worse and died before the house officer could reach him

Autopsy The body was that of a thick set middle aged man with deep cyanosis of the face and upper trunk The neck and temporal veins stood out plainly There was moderate edema of the lower legs and feet The curvature of the spine extended to the mid right chest wall and the antero-lateral surfaces of the vertebrae touched the ribs but there was no adhesion between them From there the spine turned sharply to the left and lay almost transversely until it passed the mid line to the left in the upper lumbar segment The lungs were small and pink and had the appearance of children's lungs There was a small patch of local atelectasis on the anterior surface of the right upper lobe No emphysema was found The pericardium was normal and the heart lay to the left of the mid chest The heart weighed 350 grams and was enlarged only in the right ventricle, the

capacity of which was 3 times normal and its walls were thickened to 8 mm. The columnae carnae of the right ventricle were hypertrophied. The left ventricle wall measured 15 mm. The heart valves were entirely normal. The aorta followed the tortuous course of the spine but showed no changes in caliber. The pulmonary artery was normal. The liver seemed enlarged and weighed 1800 grams. The remainder of the organs were normal. The kidneys weighed 200 grams each. Microscopic examination showed passive congestion of the lungs, liver and kidneys. The heart muscle and coronary vessels were normal. The pulmonary artery showed slight diffuse thickening of the intima and the media showed some loss of elastic tissue.

Case 4 M S, female, aged 30. Onset of right dorsal kyphoscoliosis at the age of 18. Dyspnoea on exertion. Death in respiratory failure 72 hours after operation for branchiogenetic cyst.

This 30-year-old unmarried American girl entered the hospital on March 5, 1936 for the removal of a branchiogenetic cyst that had been in the left neck for several years. She had always been a frail girl, the sixth in a family of eight, and about the age of 18 the deformity of the spine began. This was not improved by wearing casts and appliances. Her weight never exceeded 85 pounds and her height was 5 feet 5 inches. The examiner described a very thin girl with a marked right mid-dorsal kyphoscoliosis. In his opinion the heart was normal although the chart shows the pulse rate varied between 90 and 108 for the two days before operation. The blood pressure was 115/80.

On March 6, after a pre-operative medication of morphia gr $\frac{1}{8}$, she was anesthetized for 48 minutes using 210 c. c. of ether in a gas-oxygen-ether mixture. During this time the cyst was removed from the left neck and the anesthetist commented that the respirations were shallow and irregular. During the night after operation the patient twice received morphia, gr $\frac{1}{8}$, and at 7:00 A. M. on March 7th she was found almost dead of respiratory failure. The pupils were pin point. She was given stimulants and made to breathe a mixture of oxygen and carbon dioxide. Further morphia was forbidden. She continued in a precarious state, in the next 48 hours the pulse rate gradually increased to 148, the respiratory rate remained about 28 and she died 72 hours after the operation, evidently in pulmonocardiac failure precipitated by morphine. Unfortunately no laboratory studies of importance were done. An autopsy was not permitted.

Case 5 M N, female, aged 25 Right mid-dorsal kyphoscoliosis from poliomyelitis Onset of 8 years and appearance of fatigue, dyspnea and fainting attacks 13 years later Gradual increase in symptoms with orthopnea and persistent tachycardia

A 25-year-old single girl who had poliomyelitis at the age of 8 years. Although she had been kept in bed for one year and then allowed up only when wearing a spine brace, a gradual deformity developed and by the age of 13 she had a severe right mid dorsal kyphoscoliosis. The right arm had been completely paralysed and the left leg was atrophied and shortened. She walked with difficulty due to equinus deformity of the feet. Despite these handicaps she had been able to do light house work until the age of 21 when she first noted fatigue and sudden feelings of great weakness. Several times she had quietly fainted. These fainting attacks increased in number and she often had to lie flat for relief. Lying on her left side caused palpitation and discomfort. She complained so much that an orthopedic surgeon thought that she had an anxiety neurosis and referred her to the psychiatric clinic in the outpatient department in May, 1936.

In June, 1936, she was taken to the laboratory for the tests listed in the tables and while recumbent and after breathing 12 per cent oxygen for a period of 12 minutes she became cyanotic, pulseless and comatose. After a few seconds a feeble slow pulse returned and she very gradually recovered. Further tests were abandoned and she rested at home until July 3, when she entered the orthopedic service for an operation for fusion of the right wrist and tendon transplants. This was done in 2 hours under avertin and gas-oxygen-ether anesthesia with preoperative nembutal and atropine. Recovery was uneventful except that she continued with a tachycardia of 100 to 110 and a mild dyspnea that was eased by sleeping on 2 pillows.

When last seen on January 8, 1938, she was about the same, having only occasional attacks of weakness that were relieved by lying down.

Physical examination showed an undernourished, sallow and rather listless girl with a severe, right, dorsal kyphoscoliosis that had produced marked deformity of the thoracic cage causing the left ribs to be pushed deep into the pelvis. The heart did not seem enlarged and the sounds were rapid, regular and of fair quality. The blood pressure was 118 systolic and 80 diastolic. There were no signs of congestive failure. Fluoroscopic examination of the chest on April 6, 1937, showed the heart in the middle of the chest and it appeared enlarged to the right and wide in the antero-posterior diameter, the right diaphragm showed an excellent excursion while the left moved very little. An electrocardiogram showed a normal

rhythm, rate 110, the only abnormality was the absence of the Q wave in Lead IV. The difficulty of determining accurately the position of the heart makes Lead IV of doubtful value in these cases.

Case 6 L S, male, aged 17 Right and mid-dorsal kyphoscoliosis from poliomyelitis Onset at age of 13, rapidly progressive with compression of left chest Dyspnea, tachycardia and fatigue appeared at age of 15

This 17-year-old boy was well until the onset of poliomyelitis at the age of 11, then he was in the Children's Hospital for 2 months. In the 2 years after this illness he developed a right sided, high dorsal and cervical kyphoscoliosis that was little helped by the wearing of braces. The left shoulder, arm and hand became atrophic and weak. In 1933, 3 years after the poliomyelitis, he was transferred to the Massachusetts General Hospital and in March, 1934, a spinal fusion was carried out. Dyspnea had troubled him as the scoliosis progressed and it was quite severe by the winter of 1936. A second flight of stairs would cause distressing shortness of breath. No palpitation, edema, asthma, fainting attacks or cyanosis had been noted. In recent months he prefers to remain in the house, much of the time on a couch.

Physical examination showed a fairly well nourished, tall young man who had a marked degree of right dorsal kyphoscoliosis with subsequent deformity of the left chest so that it was flattened and tilted with the lower ribs resting in the pelvis on the left side. He breathed rapidly and largely with the aid of the abdominal muscles, there was very little excursion of the ribs. The neck veins were not prominent. The heart measured 8 cm to the left in the 4th and 5th interspaces and 4 cm to the right of the sternum. The blood pressure was 132 systolic and 90 diastolic. The sounds of the heart were regular, rate 88, and rather forceful with the aortic and pulmonic second sounds of equal intensity. No murmurs were heard. On lying down the pulse rate dropped suddenly to 68 and he was more comfortable. The chest was rotated to the right and the left chest was flattened while the right posterior chest bulged out in a sharp angle. Inspiration was carried out largely with the diaphragm and with each breath the right chest wall suddenly fell inward. Percussion over the right chest was resonant and the breath sounds were normal. Over the compressed left chest percussion was impaired, the breath sounds were diminished and occasional sibilant râles were heard. The abdomen was remarkable only for its muscular development.

On August 4, 1936, fluoroscopy showed a rapid heart action, rate 100,

and definite enlargement of the right side of the heart, there was little rotation and the heart was in mid chest. An electrocardiogram taken at this time showed a normal tracing. When last seen on May 19, 1937, his condition was about the same and he remarked that he was sleeping better without pillows. The arm to tongue circulation time (sodium dehydrocholate) was found to be 12 seconds.

Case 7 W C, male, aged 38. Right mid-dorsal kyphoscoliosis from probable poliomyelitis. Onset of deformity at 18 years. Asthma at 30 and later palpitation, dyspnea, orthopnea and fainting attacks on exertion.

A 38-year-old furniture mover who had been normal until the age of 18 when, without known illness, his spine began to curve to the right. His curvature progressed so that in a few years he had a marked kyphoscoliosis between the 5th and 11th dorsal vertebrae. He continued to lead a vigorous life until the age of 30, when he began to cough and soon had asthma. Dyspnea was also present and severe asthmatic attacks troubled him each week. Cyanosis of the face was observed during these attacks. He continued in this state for several years, obtaining only temporary relief from adrenalin of which he said he took as much as 8 cc. in a single night. The cough became loose and he raised mucoid-yellowish sputum. At the age of 36 he first noted palpitation and the following year he had his first attack of dyspnea, cyanosis and loss of consciousness. These episodes were brought on by moderate exertion and were not relieved by the adrenalin. After a few of these experiences he gave up walking even short distances so that in the last 2 years there have been fewer attacks. In the last 10 years he has had pneumonia 3 times on the right side and each time the disease has been more severe.

Physical examination showed a short, powerfully built man with a marked right mid-dorsal kyphoscoliosis that deformed the thoracic cage by tilting and compressing the left chest so that the lower ribs were below the iliac crest. The anterior chest wall was increased in diameter and there was definite bulging of the lower right chest. The veins of the neck, face, arms and trunk were prominent. The lungs were resonant but the sounds were diminished with occasional sibilant rales. The heart outline was enlarged slightly, being 9 cm. to the left in the 5th interspace. The right border of dullness was at the right sternal border. The sounds were rapid, 100-110, regular and of rather poor quality. The second pulmonic sound was accentuated. The point of maximum impulse was just below the xiphoid. The blood pressure was 96 mm. systolic and 66 diastolic.

Fluoroscopic examination of the heart and lungs on August 8, 1936, showed definite enlargement of the heart, particularly in the region of the right ventricle and auricle. The rate was rapid and the pulsations of the heart were diminished in amplitude. An electrocardiogram at this time showed no abnormalities.

Case 8 J G, female, aged 27. Right dorsal kyphoscoliosis. Poliomyelitic. Onset of deformity at 8 years and process complete by the age of 17. Dyspnoea on exertion for 10 years. Nocturnal attacks of smothering and precordial distress for two years.

An unmarried Italian American girl of 27, whose family first noted that she carried the right shoulder higher than the left at the age of 8. Despite frequent visits to the out-patient department of the Massachusetts General Hospital and the wearing of casts and braces her deformity increased so that by the age of 17 the process was complete. She was left with a marked right, high dorsal kyphoscoliosis, left lumbar scoliosis and marked rotation of the chest with the ribs on the left pushed into the pelvis. Increasing pain over the crest of the left ilium and shortness of breath led her to return to the hospital at the age of 24. At that time she was sent into the hospital and on April 24, 1934, a fusion of the lumbar vertebrae was performed. Convalescence was uneventful and she remained fairly comfortable in hyperextension. When examined her blood pressure was 126 systolic and 86 diastolic and her pulse rate was 88. The second pulmonic sound was slightly accentuated. On May 15, under avertin gas-oxygen anesthesia, a fusion from the seventh cervical to the eleventh dorsal vertebrae was carried out. Throughout the operation the pulse rate increased steadily, reaching over 130, and the blood pressure fell too low to read so that at the end of the second hour she was in shock, necessitating a transfusion. Recovery was gradual, the chart showing a prolonged period of tachycardia. She was discharged June 1 to a convalescent home and there remained in a plaster shell for three months.

An electrocardiogram on January 31, 1936, showed a normal rhythm, rate 90, with a normal Lead IV. The vital capacity on the same day was checked at 800 c.c.

When next examined, April 19, 1937, she complained of continued attacks of dyspnoea on exertion and about every week or two she had been awakened by attacks of a smothering sensation and severe precordial distress. There had been occasional palpitations and a rapid heart action had been noted a few times in the evenings. There had been no edema,

cough or fainting The spinal fusion had fixed her position so that the ribs no longer painfully projected into the pelvis The examination showed she was four feet, five and three quarters inches in height and weighed ninety pounds She had a severe, right, high dorsal kyphoscoliosis, left lumbar scoliosis and rotation of the chest to the right There were scars of the operations over the vertebrae The chest was clear except for a few crepitant rales over the right base The heart sounds were regular, rate 80 and of fair quality without murmurs The second pulmonic sound was accentuated, equalling the second aortic sound The heart sounds were well heard over the left back The blood pressure was 128 mm systolic and 90 mm diastolic There was mild dyspnoea with a respiratory rate of 24

Fluoroscopy showed clear lung fields and a heart shadow that seemed at the upper limits of normal in size On expiration there was marked elevation and increase in the transverse diameter of the heart shadow The venous pressure was normal (7-8 cm of blood-direct method) The arm to tongue circulation time with sodium dehydrocholate was 13 and 14 seconds (normal) The ether time was 7 seconds (normal)

Case 9 R B, an 18-year-old single school boy with a severe funnel chest and low right dorsal and lumbar kyphoscoliosis Limited activity with dyspnoea and tachycardia for one year

This 18-year-old American school boy was well until about the age of five years when it was first noted that he had a funnel chest, presumably from rickets He also suffered at this early age from frequent colds and asthma and had a suppurative adenitis of the left neck At the age of six years a right dorsal scoliosis was just noticeable At that time the examination showed a rapid heart rate with a soft systolic murmur His vital capacity was then 800 cc For several years he was given postural and breathing exercises and a back brace was worn These measures caused no appreciable improvement and by the age of thirteen he had a marked funnel chest and a severe right dorsal and lumbar kyphoscoliosis At the age of 15 it was determined that he had only seasonal hay fever due to ragweed He continued to be troubled with colds and occasional bronchitis

By the age of sixteen his kyphos had increased and pain at the apex of the deformity caused him to return to the hospital Because of this pain a fusion from the second lumbar to second sacral vertebrae was carried out on February 18, 1935, under gas-oxygen-avertin anesthesia He

stood this procedure very well. His vital capacity then measured 2100 cc. At this time Dr. E. D. Churchill examined him and felt that he had no cardiac complication as his heart lay well to the left and was not pinched between the sternum and the spine.

He led a fairly active life, graduating from high school in 1937, and his asthma troubled him very little. However, for the past year he has been rather listless, preferring to sit at home and read. Dyspnoea on exertion has been mild. He sleeps well without a pillow.

When last seen September 22, 1937, he was less active than usual and was noticeably short of breath on walking. Physical examination showed a rather pale young man with a deep excavation of the sternum and a high, right, dorsal kyphoscoliosis with a marked compensatory left lumbar scoliosis. By fluoroscopy the heart lay entirely to the left of the sternum and in a nearly horizontal position. Its action was vigorous and rapid, with a rate of 120, and the right side did not appear to be enlarged. The heart sounds were regular and rather forceful with marked accentuation of the second pulmonic sound. The blood pressure was 108 systolic and 84 diastolic. The lungs were clear except for a few crepitant rales over the right base which was the area of greatest compression. After resting, the vital capacity was 1900 cc. An electrocardiogram was taken and showed a sino-auricular tachycardia, with a rate of 120, the T wave was diphasic in all leads and there was slight axis deviation. The left axis deviation had appeared since the previous tracing in August 1936. He was then made to walk up two flights of stairs and his pulse rate increased to 160 and respiration to 32. After two minutes rest the pulse was 138. He was definitely fatigued by this slight exertion.

Case 10. A. P., female, aged 49. Right dorsal kyphoscoliosis, ? poliomyelitic. Onset of deformity in childhood. Active life bearing 8 children. Onset of fatigue and some dyspnoea after the age of 45.

A 49-year-old married housewife with a severe right dorsal kyphoscoliosis that had been acquired in her childhood. The curvature involved chiefly the 7th to the 10th dorsal vertebrae. She had been well and active, bearing eight children of whom five are living and well. Her chief complaint was fatigue, weight loss and having some dyspnoea on exertion or emotion. There had been no cyanosis, palpitation, edema or pain. On one occasion in the past she had a mild bronchopneumonia.

Physical examination showed an active, middle-aged woman in no distress, but with a severe, high, dorsal kyphoscoliosis. The heart was diffi-

cult to outline, but the left border of dullness seemed to lie 6 cm to the left in the 5th interspace. The right border of dullness was 4 cm to the left in the 6th interspace. The heart sounds were slow, regular and of good quality without murmurs. The second aortic sound was accentuated. The blood pressure was 126 systolic and 86 diastolic. Although the angulation of the spine was to the right, there was little compression or distortion of the left chest. The lungs were resonant but a few crepitant rales were heard at the right base.

Fluoroscopic examination of the chest on August 7, 1936, showed no evidence of cardiac enlargement. The heart was in good position and the contours of the right side appeared normal. An electrocardiogram showed ventricular premature beats, rate 95, slight left axis deviation. The T wave in lead 1 was flat and the Q wave in lead 4 was present.

This patient continues an active life about her home and her symptoms may be secondary to her economic status.

Case 11 I P, female, aged 22. Left dorsal kyphoscoliosis after poliomyelitis. Onset at 10 years and deformity complete at 20, since then dyspnea, fatigue and weakness. Pneumonia in compressed lung.

An unmarried Swedish American girl, 22 years old, who had been well until the age of 8 when she had poliomyelitis. About 2 years after this event a mild left dorsal scoliosis developed. This was structural in type but despite the long use of corrective jackets and casts the deformity increased until by the age of 20 she had a severe left dorsal kyphoscoliosis with the trunk twisted and tilted to the left. From the age of 20 to 22 she had dyspnea on exertion but there was no palpitation, cough, precordial pain or edema. However she remarked that she could sleep comfortably without a pillow.

Physical examination showed an undernourished but bright faced girl sitting up in no distress but her breathing was rapid and almost entirely diaphragmatic in type. There was no cyanosis, cough or clubbing of the fingers. There was a marked deformity of the chest. The entire dorsal spine was angulated toward the left and the left chest was flattened and compressed and over the left base rales were heard. The heart outlines could not be made out but the sounds were rapid, 96, regular and of fair quality. The second pulmonic sound was rough and markedly accentuated. The blood pressure was 98 systolic and 70 diastolic. The remainder of the examination was not remarkable.

An hour after the tests listed in the tables she complained of great weak-

ness and quietly fainted. She was in a grave state with pallor and bradycardia and was semi comatose for over an hour. She was taken to the hospital and gradually recovered in 24 hours but she was exceedingly fatigued for several days thereafter. In January and February, 1937, she was ill at home with a left sided pneumonia and convalescence from this was very slow. She attends the Industrial School for Crippled Children but is so weak that she often spends most of the day on a couch.

Fluoroscopic examination of the chest showed slight but definite enlargement of the right heart that was best seen in the oblique view. The diaphragms moved fairly well, the right being flattened. An electrocardiogram showed a normal rhythm, rate 110 and the only abnormality was a very slight left axis deviation.

Case 12 W D, male, aged 31. Left mid-dorsal kyphoscoliosis after poliomyelitis. Onset of deformity at 8 years. Deformity complete by age of 20. Leads a quiet life with little dyspnea, no compression of left chest. Compared with normal twin brother.

A 31-year-old man who had poliomyelitis at the age of 8 years and subsequently developed a left sided mid-dorsal scoliosis with rotation of the chest to the right and compression of the right lower thorax. He continues to wear a brace. At the age of 21 a fusion from the seventh cervical to the eighth dorsal vertebrae was performed in the hope of arresting the deformity. However it has slowly increased, leaving him with a severe left sided kyphoscoliosis. There was atrophy and weakness of the left arm and hand. He had no complaints and insisted that he could climb 6 flights of stairs without undue dyspnea. However he leads a very inactive life and his family complain that he always sits about indoors.

Physical examination showed a healthy appearing young man of good color and with the deformity described above. The left chest seemed to be increased in size due to elevation of the left shoulder and increase in the antero-posterior diameter. The left border of cardiac dullness was about 6 cm from the mid-sternal line. The heart action was rapid, 100, and regular, and the sounds were of good quality with a faint systolic murmur heard at the apex. The second pulmonic sound was accentuated. The blood pressure was 110 systolic and 80 diastolic. The chest was clear and resonant except for a few rales at the right base. Fluoroscopic examination showed a normal sized heart in mid-chest position. An electrocardiogram taken on Feb 11, 1936 showed a normal rhythm, rate 96, and a slight right axis deviation. The remainder of his studies appear in the tables.

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SULPHUR THERAPY IN ARTHRITIS

WITH A REVIEW OF THE LITERATURE¹

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During the past five years, a wave of sulphur therapy has inundated the field of the rheumatic diseases. It has been suggested that because of the increased demands for sulphur by the body for detoxication of injurious metabolites, the organism is in negative sulphur balance. Investigators have suggested that the lowered cystine content of the nails in arthritis is a manifestation of this. Accordingly, sulphur has been given in various forms (orally, parenterally, as baths, (60, 65) ointments, etc.) as an adjuvant in the treatment of some of the rheumatic diseases. Varying success has been reported by clinicians with this form of therapy. It is my purpose to review the literature and present some results of five years personal experience with sulphur therapy in clinical and experimental fields.

Sulphur is an ancient medicinal agent. Pliny (28)[†] used it in a number of diseases. Among the early Greeks, it was called "Therion," or divine (55), to waters containing it beneficial effects were ascribed (34). "Sulphur and molasses" is an old household remedy for rheumatic diseases and a spring tonic. Alchemists employed it in their attempts to transmute metals into gold and silver (72). It has value in agriculture and horticulture in aiding growth of vegetation and in checking parasites.

The introduction of a colloidal sulphur preparation (15) in 1888 was followed by extensive investigation of this product (51, 45A). Colloidal sulphur was first used in the treatment of arthritis by French and German clinicians (45, 47). It was later suggested on experimental evidence (6, 8, 80, 69A) that the arthritic individual had a disturbed sulphur metabolism. Recently the cystine content of the

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finger nails has been reported markedly reduced in patients with arthritis. This has increased the use of sulphur in arthritis.

Sulphur metabolism in the normal individual has been well reviewed by various workers (56, 36, 37, 16, 24). The data concerning sulphur metabolism in common diseases (pneumonia, diabetes, nephritis, syphilis, goiter, acute infections, etc.) are meager. A generalized sulphur deficiency has been suggested in pellagra with extensive dermatitis and in rheumatoid arthritis, based chiefly upon a lowered cystine content of the finger nails in these conditions, if so, it has not been determined whether there is an increased requirement, decreased absorption from the intestine, increased destruction of sulphur or disturbed assimilation of sulphur in the body. It has also been suggested that there is a deficiency of sulphur in joint tissues (40) and that the chondroitin sulphuric acid in the joint cartilages of the patient with rheumatoid arthritis may be diminished.

PHARMACOLOGY

Sulphur is insoluble in water, nearly insoluble in alcohol, slightly soluble in fat solvents and oils and freely soluble (up to 45 per cent) in carbon disulphide. It may be absorbed through the intact skin (55) for there was a marked increase (87 per cent) in the total sulphur content of the blood serum 12 hours after the application of 10 grams of sulphur ointment (USP) to the skin (48). The sulphur content of the blood was also increased by sulphur baths (53). Sulphur baths (55) and naturally occurring hot sulphur springs have long been employed by sufferers from arthritis with reported benefit.

Claims for beneficial pharmacological action of sulphur in arthritic patients are vague. It has been suspected that (71) sulphur contained in organic compounds, such as cystine, cysteine and glutathione may act as a detoxicating agent in the body and it is known that glutathione "plays an important rôle in cellular respiration, oxidation and reduction and in the stimulation of enzymotic activity." The sulphur in glutathione is rather easily liberated, and it has been supposed that a function of this compound may be the liberation of active sulphur to detoxicate injurious material. However, the glutathione content of the blood was within normal limits (64) in rheumatoid and osteo-arthritis, in bursitis and in peri-arthritis.

Certain injurious substances when combined with sulphur become less toxic and are eliminated in combination with it. For example, the intestinal poison indole is oxidized within the body to indoxyl, which is then combined with sulphur and excreted as indican.

Sulphur, like oxygen, has a powerful affinity for many other elements. With valences varying from 2 to 6, it has a high combining power. It has been suggested that certain therapeutic effects of sulphur result from the splitting up of polysulphides into elementary sulphur at foci where localized inflammation exists. This may be due to a higher concentration of hydrogen ions at the site of an inflammatory process.

The cystine content of the finger nails has been found decreased in patients with rheumatoid arthritis and increased toward normal following improvement under sulphur therapy. It has been supposed that an intoxication draws on the sulphur of the body and withdraws it from its normal locations (such as the nails). The increase of cystine in the nails in arthritic patients after sulphur therapy has been taken as evidence that the body needed sulphur either to combine with the injurious material or to stimulate the general defense mechanism of the body.

There is some indirect evidence (26) that sulphur increases the catabolism of proteins within the body. The effectiveness of colloidal sulphur in arthritis has been attributed by some to changes in ill-defined metabolic processes rather than to any direct local effect on the inflamed tissues.

Others consider the results obtained by parenteral sulphur therapy as entirely non specific in nature and the effect of the slight fever and leukocytosis which may follow such injections. Inasmuch as some of the so-called colloidal sulphur preparations contain considerable amounts of "protective colloid" protein, this latter may be of importance in the results obtained.

When taken by mouth, sulphur frequently increases intestinal peristalsis (72) and produces softer and more frequent bowel movements. Most of the sulphur passes unchanged through the bowel (49) and is excreted with the feces. It readily reacts with proteins in alkaline medium producing sulphides which are bactericidal, irritant, and laxative. Inorganic sulphides are active and poisonous

agents, even small amounts in the circulation would be expected to irritate the cortex or medulla

Studies on urinary sulphur excretion in arthritis have been contradictory In a study of 18 cases of atrophic and 41 of hypertrophic arthritis as well as in 20 normal individuals the urinary sulphur excretion was normal (67) Others (5, 59) have noted an increase in the urinary output of sulphur

A polymorphonuclear leukocytosis was noted (24a, 49) following parenteral administration of colloidal sulphur both in animals and in man A moderate degree of fever has followed (43) the use of certain sulphur preparations parenterally

The effects of parenteral administration of sulphur have been studied in guinea pigs given the drug intraperitoneally, in rabbits intramuscularly, (42, 57, 78) in dogs intravenously and intramuscularly (78) and in man (39, 42) No evidence of harm has been reported in clinical doses The toxicity of parenterally administered sulphur seems to depend (78) upon its dispersion and upon the speed of the intravenous injection Toxic effects are due to the rate and amount of formation of hydrogen sulphide (8) In guinea pigs (78), the toxic dose given intravenously was 30 to 40 mg per kg, and intramuscularly in oil, 220 mg per kg In rabbits the toxic dose varied from 6.6 mg per kg injected in 5 seconds to 15 mg per kg injected in 104 seconds In dogs, large repeated doses over long periods produced no harmful effects

A more or less maintained leukocytosis occurred in rabbits (57) receiving daily injections of sulphur in oil, the leukocytosis began several days following the onset of treatment and persisted as long as the treatment was continued It was due to increase in neutrophils The bone marrow of these animals showed marked hyperplasia varying with the amount of sulphur used, in some cases this was evident macroscopically The leukoblastic tissue was most affected but erythroblastic elements and megakaryocytes did not entirely escape There was also a definite diminution in the number of fat spaces and a corresponding increase in cellular elements

In a number of patients treated with sulphur (57) a shift to the left tended to become more marked with repetition of the injections Injections of sulphur in oil intramuscularly (42) produced a high fever lasting for 36 to 60 hours, with a variable elevation of the pulse,

a vasomotor and diaphoretic response less marked than in fever from typhoid vaccine and a marked polymorphonuclear leukocytosis. In some instances, leukocytosis was maximal 24 hours after parenteral sulphur therapy (57), while in others, leukocytic crises did not occur until after the seventh injection of sulphur (39).

No instance of sensitivity to sulphur was found in three studies of patients with skin diseases (46, 48, 51). Anaphylactoid or colloidal shock (26, 30) may follow the intravenous administration of colloidal sulphur preparations. Urticarial and scarlatiniform eruptions (61) have followed intravenous sulphur therapy. Exfoliative dermatitis with recovery has been reported following (76) within 24 hours after the first intravenous injection of colloidal sulphur. The use of sulphur pastes in nurslings with scabies has resulted in severe disorders and even in death (54). Reactions have been noted following the use of sulphur orally (77A) or byunction (50A).

Normally there is rarely as much as one per cent of cystine in the diet (72). Ten per cent of free cystine in the diet of rats acted like a powerful poison (74) producing marked injury to the kidney and liver, while the addition of 5 per cent of free cystine to the basal diet produced excellent growth. In long continued feeding experiments (330 to 360 days), no renal injury was produced when 1 per cent of free cystine was fed to rats in the diet (the rats being 30 days old at the start of the experiment). 0.3 to 0.9 per cent of free cystine in the diet was nephrotoxic to young rats 60 gm or less but not to rats of from 80 to 90 gm.

It has been suggested that the suprarenal gland is concerned in normal sulphur metabolism. After removal of the suprarenal capsule (85), the sulphur content of the skin rose from 25 to 100 per cent.

The Council on Pharmacy and Chemistry, of the American Medical Association, has not yet accepted (11, 12, 13, 13A) any of the preparations of "colloidal sulphur" now on the market. "Sulisocol," "Streptocoll" and "Sulphocol" have been submitted to the Council but have not been found acceptable. The Council has stated such a product was not acceptable "because of lack of evidence of its therapeutic value, since such products have been in use for many years without having their therapeutic value recognized by the leaders in medicine who are concerned with the treatment of arthritis."

SULPHUR AND CYSTINE CONTENT OF NAILS

Oral administration of sulphur has been recommended (23, 31) in the treatment of dystrophy of the nails. The sulphur in the nails, as in hair, is almost entirely in protein combination as cystine (69). Cystine contains 26.7 per cent of sulphur.

The sulphur content of the nails in healthy adults averaged (31) 3.2 per cent (2.9 to 3.6 per cent). In eight patients with psoriasis, the sulphur content of the nails averaged 2.46 per cent, the more pronounced the nail involvement, the lower was the sulphur content in this series. In the spoon shaped nails of 5 negroes with pulmonary tuberculosis, the sulphur content averaged 2.38 per cent (31), in 5 patients with chronic rheumatoid arthritis, the sulphur content varied from 2.0 to 2.8 per cent. In inoperable carcinoma with marked cachexia, the sulphur averaged 2.6 per cent, a similar figure was obtained in patients with prolonged fever.

Some workers (31) have concluded that the determination of the sulphur content of the nails is of no value in the study of diseased nails. Hydrolyzed wool was given orally in the treatment of patients with pathologic nails, producing clinical improvement only in patients with congenital dystrophy of the nails.

In normal nails, the cystine content accounted for practically all of the sulphur of the nail (97–98 per cent (71)). In the nails of arthritic patients, the cystine sulphur did not closely parallel the total sulphur, and was occasionally much below it. In twelve patients with arthritis, the percentage of cystine sulphur to total sulphur varied from 76 to 98.

In normal individuals the average cystine content of the nails was 11.7 per cent (71) (varying from 10.3 to 13 per cent). In patients with arthritis, various observers (2, 3, 50, 71, 83) have noted a decrease in the cystine content of the finger nails, in patients with rheumatoid arthritis, the cystine content averaged 9.5 per cent. The cystine content of the nails has also been found low in pellagra and somewhat decreased in pulmonary tuberculosis (35, 75). Cystine decrease seems to be a concomitant of chronic illness in general and not necessarily of rheumatism (62).

Measurement of cystine content of finger nails has been very disappointing in our hands. We have examined the cystine content of

the finger nails in several hundred normal individuals, and have made repeated determinations in more than 100 patients with rheumatoid arthritis and 100 with osteo-arthritis, as well as in other forms of rheumatic disease

We have observed that the range of normal variation is greater than reported. In 215 normals, there was a normal distribution, about a median of 9.7 with a quartile dispersion between 8.8 and 10.6. Furthermore, although a majority of the patients with rheumatoid arthritis showed lowered cystine content of the nails, a very large percentage fell within our range of normal controls. In addition, lowered cystine content was also found in the nails of elderly individuals with osteo-arthritis and also in some persons without any evidence of arthritis. The cystine content of the nails did not aid in determining which patients would respond to parenteral sulphur therapy, and in some of the patients showing the greatest clinical improvement on sulphur therapy, the lowered cystine content of the nails did not rise. A detailed summary of these observations will form the basis of a separate communication.

The methods available for the determination of cystine in the nails include the one (73) or six hour (70) Sullivan methods, the Okuda (52), the Folin (17), the Shinohara (68), etc. The accuracy of the Sullivan method for cystine determinations in protein hydrolysates in which the proportion of cystine to other amino acids is small has been questioned (33). Many reducing agents such as ascorbic acid, adrenalin, hydrogen sulphide and compounds producing sulphides under alkaline conditions produce low results (1) by the Sullivan method. Improvements in this method have been suggested (41, 58). The modification of the method proposed by Sullivan in which alkaline instead of aqueous sodium cyanide is used minimizes interference.

RESULTS OF SULPHUR THERAPY IN ARTHRITIS

Most of the reports in the literature on the results of parenteral sulphur in arthritis are favorable. One author goes so far as to say (79) that in more than 200 patients with atrophic arthritis treated with sulphur "every case showed excellent clinical improvement, all except six were discharged from the hospital with complete arrest of the active symptoms." Unfortunately, our own results were not as favorable as these.

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Good therapeutic results have been reported by various workers (2, 32, 50, 27, 4, 66, 45, 61, 79, 80, 83, 84, 7A, 9A, 23A, 45B, 62A, 76A) employing intramuscular or intravenous injections of sulphur in arthritis. Some of these results are as follows

1 Hawls, Gruskin and Ressa (61) In 20 patients with rheumatoid arthritis whose cystine content of the nails was under 12 per cent, 60 per cent were improved, in 13 patients with rheumatoid arthritis with a nail cystine content of 12 per cent or above, only 23 per cent were improved. In 28 patients with a mixed form of arthritis and with a subnormal nail cystine, 57 per cent were improved, in 13 such cases with a normal cystine content (above 11 per cent) only 31 per cent were benefited. In 19 instances of osteoarthritis with subnormal nail cystine, 63 per cent were improved while when the cystine content was normal, only 14 per cent were aided. Thus, it may be noted that regardless of whether the individual has rheumatoid, osteo-, or a mixed form of arthritis, sulphur therapy was equally beneficial provided the cystine content of the nails was subnormal. In the 33 patients whose cystine content was normal, only 24 per cent were benefited by sulphur therapy. In some of these patients whose cystine content was markedly subnormal at the beginning of treatment, this was raised to within normal limits at the end of the treatment without any improvement in the arthritis.

In these patients no other treatment was given than colloidal sulphur in doses varying from 20 to 30 mg twice weekly, intravenously or intramuscularly. Some of their patients did not tolerate the larger doses. The authors also treated a control group of 25 patients, consisting of 8 individuals with rheumatoid arthritis, 7 with osteoarthritis and 10 with mixed arthritis with placebo medication, such as intravenous injection of Ringer's solution. The number of patients benefited by such placebo medication was not mentioned although it was stated that there was no significant change in the non-filament cell count or in the mean sedimentation rate following placebo therapy. In patients given parenteral sulphur, the mean sedimentation rate was 23.5 mm before and 16.9 mm after treatment while the mean non-filament cell count was reduced from 16.1 per cent to 13.9 per cent.

These authors found almost no correlation between the sedimentation rate and cystine content of the nails in this group of patients. Such studies were made in 200 cases so that the results should be more conclusive than those of Argy (3) who studied only 23 cases and reported that "at least on the average, an inverse ratio between cystine content of the finger nails and sedimentation reaction of the blood does exist in arthritis."

2 Clark (9) used relatively large doses (averaging 600 mg per course) of colloidal sulphur intravenously in the treatment of 20 selected cases of mixed and hypertrophic arthritis, averaging 53 years in age. "All of the cases were objectively improved as judged by subsidence of swelling, relief of muscle spasm, decrease of thickening of joint capsule (where palpable), disappearance of any increased local temperature, decrease in tenderness, increase in, or return to normal range of motion, and decrease in deformity." No untoward reactions were noted in any of these cases. However, in addition to sulphur therapy, other methods of treatment were also carried out in these patients, including attention to focal infection, gastro-intestinal elimination, body mechanics, decreased carbohydrate intake and salicylates and iodides early in the therapy. The usual individual dose of sulphur averaged 60 mg and was given at 2 or 3 day intervals.

3 Woldenberg (84, 82, 81) found that 78 per cent of his patients with arthritis when treated parenterally with sulphur became free from pain after 5 or 6 injections, the muscular spasticity began to disappear and the joint effusion became less and after 3 or 4 weeks disappeared. This author used as much as 30 mg of sulphur intravenously each day on 10 successive days if the arthritis was of a severe type, of long standing with a rapid sedimentation rate and with low nail cystine. He found sulphur therapy of equal value in chronic and in acute cases of arthritis as long as pain, swelling, effusion and spasticity of muscles were present. He obtained better results in the atrophic rather than in the hypertrophic type of arthritis. The number of patients treated numbered over 200 and, in addition to the sulphur therapy, his patients were treated by eradication of focal infection, laxatives, a high vitamin, low protein diet and daily physiotherapy.

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4 Wheeldon and Main (78, 79) In a study of 50 patients with arthritis (25 atrophic and 25 hypertrophic), these authors reported concerning sulphur therapy "It can be said that every case improved subjectively in spite of the fact that all the cases were chosen because, up until that time, they had not improved under the usual accepted treatment No patient expressed any desire to discontinue the treatment because of discouragement, and at the end of the experiment practically every patient asked that this medication be continued because of the improvement he or she felt had already been gained" After a study of 892 cases of atrophic and hypertrophic arthritis, Wheeldon felt that improvement "in the subjective symptoms and objective signs may be expected following treatment with colloidal sulphur"

5 Krestin (England) (32) treated 50 cases of chronic non-specific arthritis with sulphur Injections were given intramuscularly every 5 or 6 days Five of the patients refused to continue treatment after the first or second injection Unfortunately, his patients were not well classified and no control group was used He felt that improvement appeared when there was consistent occurrence of pyrexia and leukocytosis and he postulated general stimulation of metabolic processes and of defense mechanisms Good results were obtained in 45 per cent of the group, considerable recovery in 22 per cent, partial recovery in 20 per cent and no improvement in 12 per cent In about one-fourth of the cases in which definite improvement occurred after treatment, symptoms subsequently returned, although the relapsed condition was always less severe than that preceding treatment In no instance was the disease made manifestly worse and no harmful effects were observed provided the patient was treated in a non-acute quiescent phase Treatment was not given during the acute phase of an arthritis, in elderly, feeble or emaciated patients, in nervous or hysterical patients, in very obese patients, or in those with tuberculosis or other active organic disease

The statements of others include "Sulphur is a forgotten remedy" which should be re-investigated (21), results of sulphur therapy were "disappointing" (25), results were helpful in a small series of patients (63, 44), no definite improvement in 50 or 60

cases (29), "absolutely without effect" in 12 cases (14), improvement in 75 per cent of 60 unselected cases of chronic non-specific arthritis and rheumatoid conditions (66), and little or no improvement (7B, 23C, 75A, 23B, 61A)

Unfortunately most of the work presented to date seems to be uncontrolled. In one series an internist had treated over 1500 cases of atrophic and hypertrophic arthritis with sulphur and had noted no untoward reactions of any kind, local or general, except slight headaches in a few (80). In the treatment of 200 patients the following untoward symptoms occurred in a few (61): urticaria, a scarlatiniform reaction, nausea and occasional vomiting, abdominal cramps and diarrhea, severe fatigue, headache, nervousness, generalized muscular soreness, insomnia, and loss of appetite, some with larger doses developed chills and fever, appearing in 2 to 4 hours, confining the patient to bed for 24 hours. Most of these reactions followed intravenous use of the drug, very few reactions occurred following intramuscular injections.

From reports in the literature it has been inferred that from 45 to 100 per cent of patients with rheumatoid arthritis have been greatly improved by sulphur therapy parenterally. This improvement has consisted of decrease of periarticular swelling, increased mobility of the joints, and diminution or absence of pain. Patients with hypertrophic arthritis have also been reported benefited (80).

In view of the reported increases in the cystine content of finger-nails following injection of colloidal sulphur, various workers attempted to discover whether injected sulphur can actually be utilized by the animal organism. In rats (38) and in adult mice (22) no utilization of dietary sulphur for growth was observed. It was also found (77) that colloidal sulphur given intraperitoneally to rats was not utilized either for production of cystine or for growth.

Sulphur therapy has been reported (84) of equal value in acute and chronic cases. Others (32) have obtained best results in younger patients with relatively short histories, still others (61) have reported the best results in older patients with rheumatoid and mixed arthritis, where the cystine content of the nails was frequently low. Patients with acute phases of arthritis, elderly or emaciated individuals, nervous patients, the very obese, and individuals with pulmonary tuberculosis have not stood the treatment well (32).

The method of administration and the dosage have varied widely. The intravenous dose has varied from 1 to 30 mg per day, most investigators, however, have begun with minimal doses. After the maximal dose has been reached, some individuals give 30 mg per day intravenously for 10 days (84), in addition to an intramuscular course of sulphur. Those using the intramuscular route usually employ between 5 and 25 mg per dose, and give 2 or 3 injections weekly. Improvement has usually been observed after the fourth or fifth injection, in some instances, this was delayed until after the tenth injection. A course of intramuscular injections usually consists of 15 to 20 doses.

We have observed the action of sulphur therapy in 30 patients with rheumatoid arthritis and 30 patients with osteo-arthritis over a period of more than 3 years. Patients not observed over at least a 3 year period have been excluded from this series. The diagnosis was confirmed in each patient by a careful general and arthritic history, and by physical examination, roentgen examinations, sedimentation rate, blood uric acid determination, complete blood count, urinalysis, blood Wassermann reaction, and when indicated, by Neisserian complement fixation test and other laboratory examinations. No patient in this series was completely cured of his arthritis by parenteral sulphur therapy. Almost all of the patients had a preliminary period of placebo therapy, using intravenous injections of glucose and salt solution, and intravenous and intramuscular injections of the menstruum used for the sulphur. Approximately twenty per cent of each group noted moderate subjective improvement following injections which contained no sulphur, but no objective changes in the joints were noted.

In our sulphur therapy, 3 brands of so-called colloidal sulphur were used². One-third of the patients were given sulphur intravenously, one-third intramuscularly, and one-third by the combined intravenous and intramuscular routes. Clinical results were about the same in the three groups so that in our experience, the route of administration was not important. During the periods of sulphur therapy, all other forms of treatment were discontinued.

² Sulphur was furnished through the courtesy of the Doak Chemical Co., of Cleveland, the Mulford Colloid Laboratories, of Philadelphia, and the Drug Products Co., of Long Island.

In the group with osteo-arthritis, no evidence of objective improvement and no roentgen changes were noted following the parenteral administration of sulphur. However, 50 per cent of the patients felt moderately to markedly improved during the course of therapy. The improvement usually did not persist more than several weeks following the last injection. Several of these patients noted such marked relief of pain following the intramuscular injections, that repeated courses of treatment were demanded by the patient. In this group, two instances of acute coronary occlusion occurred during the course of therapy. The author feels that although in the group of osteo-arthritis sulphur therapy may be used in elderly individuals, it should not be used in patients with cardiac disease.

In the patients with rheumatoid arthritis, objective improvement such as decreased swelling of the joints, increased mobility, decreased sedimentation rate, etc. were noted in only 30 per cent. Twenty per cent of these patients with rheumatoid arthritis improved markedly following parenteral sulphur therapy, joint swellings disappeared, mobility of joints increased, sedimentation rates returned to normal, etc. In addition, 30 per cent noted moderate to marked subjective improvement which was manifest chiefly by decreased stiffness of the joints. The remaining 50 per cent were not benefited by sulphur therapy.

We have not noticed any definite correlation between improvement in the arthritis and increase of the cystine content of the nails, nor have we been able to predict which patients would benefit most by this therapy. Several of the patients receiving most benefit exhibited a normal nail cystine at the onset of therapy. Patients receiving large doses of sulphur (20 to 30 mg per dose) improved more than those with smaller doses.

Our intravenous injections began with one mg of sulphur and increased by doubling the dose at each injection until 30 mg was reached. In some individuals daily injections were given, in others injections could be made only twice weekly. It did not seem that the greater frequency of injections was especially beneficial. We did not exceed a total of 300 mg of sulphur intravenously in any one course. Rest periods of at least 10 weeks were given between courses of therapy.

When sulphur was given intramuscularly, our dosage varied from

1 to 20 mg gradually increasing the dose at each injection. Injections were made 2 or 3 times weekly. Again, a total of 300 mg was not exceeded in any one course of therapy. When combined intravenous and intramuscular therapy was utilized, 300 mg were given intravenously over a period of 10 days, while 50 mg were given intramuscularly during the same period (giving intramuscular injections every second day).

A detailed account of our results will form the basis of a separate communication. Suffice it to say that our results were no better than, and in many instances not as good as, those obtained by other means, such as rest, physiotherapy, removal of focal infections, vaccine, etc. In view of these results, it is our opinion that sulphur should not be used in the routine treatment of arthritis unless other simpler and generally accepted methods of therapy have failed. If improvement has not been obtained under conservative therapy, cautious administration of sulphur may be indicated.

Great care must be exercised in giving colloidal sulphur intravenously, leakage of sulphur into the tissues surrounding the vein has resulted in a large area of sloughing, which is quite painful. Intravenous injections should be made very slowly. When intramuscular injections are employed, the area should be massaged vigorously following the injection to prevent the formation of painful lumps. Inasmuch as certain companies prepare separate preparations for intravenous and intramuscular use, the particular ampoule to be injected should always be examined carefully, intravenous administration of colloidal sulphur in oil (an intramuscular preparation) might prove fatal.

Forbes and Neale (18, 19, 20) have recently stressed the value of sulphur administered orally in the treatment of arthritis. These investigators found that indole, which is normally detoxicated in the body, was eliminated unchanged in the urine in patients with arthritis, they state that such an indoluria parallels the clinical condition, finally disappearing when the patient improves markedly or recovers.

Indole is normally detoxicated in the liver by oxidation to an indoxyl compound which then is combined with a sulphur radical to form indican. The authors have suggested that inasmuch as sulphur plays a major rôle in the detoxication of indole, the presence of this latter in the urine in arthritis may be an indicator of sulphur deficiency.

These workers found that 34 of 39 patients with rheumatoid, osteo or mixed arthritis eliminated indole in the urine. When 32 of these patients were placed upon a high sulphur, high vitamin B and low carbohydrate diet, marked improvement occurred in 26 of the group.

A demonstration of the toxic local effects of indole was furnished by injection of dilute sterile solutions of indole directly into the knee joints of rabbits, this resulted in the production of a severe form of chronic arthritis, with permanent damage to the joints (as has been reported with various other substances similarly injected). No changes occurred in control joints in which only the solvent was used (20). We have confirmed this work in rabbits (10).

SUMMARY

1. A summary of the literature on the use of sulphur in arthritis is presented.

2. Parenteral sulphur therapy appears to be beneficial in some cases of arthritis.

3. In our experience, it would seem that a trial of sulphur therapy is justified if routine conservative treatment produces no improvement in the arthritis.

4. Cystine determinations of the nails were of no assistance to us in judging which patients would be benefited by sulphur therapy.

5. Some evidence is presented that parenteral sulphur is not utilized either for production of cystine or for growth.

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PYELONEPHRITIS ITS RELATION TO VASCULAR LESIONS AND TO ARTERIAL HYPERTENSION

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INTRODUCTION

The interpretation of the clinical course of patients dying of uremia or of complications of arterial hypertension, in whom "contracted" kidneys are found on postmortem examination, has changed during the past few decades. From the cases formerly diagnosed as chronic Bright's disease two large groups have emerged: one in which the renal damage has been attributed to primary inflammatory processes ("chronic nephritis," "chronic interstitial nephritis," "chronic glomerulonephritis") the other in which the progressive decrease of the renal parenchyma and the functional reserve has been considered as secondary to obliterative vascular lesions and to ischemia ("nephrosclerosis," "arteriosclerotic or arteriolosclerotic kidney," "vascular nephritis," "hypertensive nephritis"). Subsequent clinical experience has indicated, however, that in a considerable number of instances, regardless of the primary cause, both types of lesions, i.e., inflammatory and vascular, are present in the same case. Furthermore, it is often difficult to ascertain, either from the clinical or from the morphologic evidence, whether the inflammatory or the vascular lesions are primary.

In the group of cases with Bright's disease in which the renal lesions are predominantly of an inflammatory nature, inadequate separation has been made between cases in which the renal inflammation is usually independent of local microorganisms and those in which the inflammation depends on bacterial invasion and pyogenic responses of the renal tissue. Thus it is only relatively recently that chronic pyelonephritis has been separated from chronic glomerulonephritis.

As early as 1882 Wagner (1) described cases corresponding to chronic pyelonephritis and in 1917 Lohlein (2) reported 3 cases of contracted kidney following pyelonephritis. Nevertheless, the nature of the course of the disease was not appreciated until recently. Thus Gyorgy (3), Haslinger (4), Schoen (5), Staemmler and Dopheide (6) and Jacoby (7) as recently as 1931 have emphasized the lack of specific information with regard to both the clinical and the structural characteristics of the disease. In the Anglo-Saxon literature, with the exception of reference to certain features of the disease by urologists (8), practically no information was available until Longcope and Winkenwerder (9) emphasized its significance in internal medicine.

Subsequently, Peters, Laviettes and Zimmerman (10) called attention to the rôle of "pyelitis" in toxemias of pregnancy

There are several reasons for this slow recognition of pyelonephritis as an entity distinctly separate from other nephropathies. Pyelonephritis is a disease with strikingly variable clinical course and structural lesions. Furthermore, a given case shows different features at different stages of the disease. As long as "pyelitis" of early childhood was considered by pediatricians as a benign and transient purulent infection of the renal pelvis, it was not suspected that this condition in its chronic stage is related to certain types of toxemia of pregnancy with apparent recovery, observed by the obstetrician, to subsequent attacks of pyuria, treated by the urologic surgeons, and to arterial hypertension of progressive severity, developing years later, and associated with impaired concentrating capacity of the kidney with but a trace of albumin and few or no white blood cells in the urine, cared for by the internist. Only when it became *sufficiently* recognized that "pyelitis" is uniformly associated with focal or diffuse inflammatory lesions of the parenchyma of the kidney, as well as of the pelvis, was it suspected that acute "pyelitis," or pyelonephritis, bears a relation to the functionally insufficient, contracted and irregularly scarred kidneys of chronic pyelonephritis. Thus Escherich (11) as early as 1894 described pyelitis as a disease of childhood, and Göppert (12) in 1908 called attention to the frequency and significance of the disease (*Volkskrankheit*). Göppert has also pointed out that in some instances following an attack of "pyelitis," pyuria, bacteriuria and other symptoms may persist for years. In 1910 Ghiemich (13) called attention to the fact that in severe cases of pyelitis there are changes in the renal parenchyma as well as in the pelvis and that under certain conditions pyelitis can become a chronic renal disease. Nevertheless, in 1930 Staemmler and Dopheide (6), in describing certain morphologic characteristics of chronic pyelonephritis, emphasized that in none of the cases which they reported was the disease suspected clinically. Thus, notwithstanding the advances made in the knowledge of the disease, there are several important aspects not yet appreciated either by physicians or by morphologists.

Our interest in pyelonephritis dates back over a period of 5 years

During this time we have observed a group of patients whose presenting syndrome was a severe degree of arterial hypertension, with or without renal failure. In several of these cases clinical and laboratory evidence did not indicate the presence of renal infection. Nevertheless, histologic studies revealed chronic or healed renal inflammation and vascular lesions such as are characteristic of pyelonephritis as well as of "malignant" nephrosclerosis. The purpose of the present communication is to summarize the clinical and morphologic features of pyelonephritis and to report on certain heretofore not well recognized aspects of the disease.

MATERIAL

A clinical and morphologic study has been made of 100 cases of pyelonephritis in various stages from the acute to the terminal chronic or healed. There were 58 males and 42 females in the group of various ages, ranging from 4 months to 78 years. Of the 100 cases studied, 86 had adequate clinical histories and postmortem examination failed to reveal other complicating renal pathology. This group was selected from a larger group of cases of pyelonephritis primarily by means of histologic examination. As the clinical course and the morphologic characteristics of acute pyelonephritis have been adequately studied in the past, we have concentrated mainly on the study of the chronic stage of the disease, as well as of the characteristics of vascular lesions occurring in chronic pyelonephritis and their relation to arterial hypertension. Hence the cases were selected on the basis of (a) whether they contributed to the understanding of the natural history of the disease, and (b) whether they showed arterial hypertension or vascular changes. Cases with neoplastic disease of the urinary tract, as well as those with evidence of primary arteriosclerosis complicated by pyelonephritis, were, with few exceptions, omitted from the special group studied. Because of the method of selection, the material does not lend itself to statistical analysis. In order, however, to answer special questions which have arisen during the course of the investigation, analysis has been made of certain features of additional cases of pyelonephritis. Similarly, groups of cases with hydronephrosis, renal tuberculosis, benign and malignant

nephrosclerosis of nonpyelonephritic origin, glomerulonephritis, renal aplasia or agenesis have been studied in order to define the differential characteristics of pyelonephritis

In all the cases studied, in addition to the analysis of the clinical and laboratory data and of the necropsy findings, a systematic histologic study of the kidneys was made. This included an estimate of the extent of the pyelonephritis. The nature of the changes in the renal pelvis was defined. The glomeruli were examined quantitatively and as to the degree and extent of glomerulitis, necrosis and sclerosis. The tubules were analyzed as to the degree of dilatation and the presence or absence of pus and colloid casts. The character of infection and inflammation in the interstitial tissue was described. In addition, in each case the arteries and the arterioles were investigated. The renal capsule and the adrenal glands were studied in detail. Vascular changes in other organs were also analyzed. Depending on the findings in the routine analysis, special studies were undertaken as will be indicated.

TYPES OF PYELONEPHRITIS

Both the clinical course and the morphologic features of pyelonephritis show considerable variation. Its diagnosis, nevertheless, offers less difficulty from a histologic than from a clinical point of view. Mainly on the basis of histologic evidence we have classified pyelonephritis into four groups, representing various stages of the same disease: (1) acute pyelonephritis (pyelitis), (2) chronic pyelonephritis, (3) healed pyelonephritis and (4) healed and recurrent acute pyelonephritis. Any of the four types may be unilateral. If both kidneys are involved the character of the process is not always the same in each. The foregoing classification includes all nontuberculous suppurative bacterial infections of the kidney associated with certain characteristic structural alterations. So called acute interstitial nephritis, because of the difference in structural changes in the kidneys, is not included, although this type of nephritis is considered by some as a special type of pyelonephritis. The classification considers neither the specific causative organism nor the mode of origin of the bacterial renal infection. Furthermore it is essential to emphasize

that unless detailed clinical data are available, in the majority of instances the diagnosis of healed and recurrent acute pyelonephritis is not feasible

Such rather simple classification seemed to us essential because in the majority of instances even the combined clinical, bacteriologic and histologic evidence fails to reveal with any degree of certainty whether we are dealing with pyelonephritis of hematogenous ("descending"), urogenous ("ascending") or lymphatic origin. Furthermore, the absence of demonstrable obstruction does not rule out physiologic disturbances of urinary flow. Contrariwise, the presence of a structural defect in the urinary tract cannot be used *a priori* as evidence for or against hematogenous or urogenous infections. Hence the more complex classifications are not applicable in practice. Indeed, from a clinical point of view certain objections can be raised even to the use of the simple classification here proposed

Acute pyelonephritis (pyelitis)

The clinical course and the postmortem findings in acute pyelonephritis are well recognized (11, 12, 13, 14, 15, 16, 17, 18, 19). Our study of this stage of the disease has failed to add significant new information. Fever with systemic response of an acute infection, pallor, pain and tenderness related to one or both kidneys, dysuria, tenesmus, pyuria, at times bacteremia, and tendency to anemia are the main clinical features. The arterial pressure is normal. Examination of the urinary tract, particularly in adults, often reveals abnormalities. Nitrogen retention does not develop in the majority of cases. Frequently the symptoms are not sufficiently specific to indicate an acute suppurative renal disease. The details of the diagnostic methods employed are outside the scope of the discussion. As a rule there is no consistent difference in the clinical symptomatology and course of pyelitis of various origins and of varied bacteriology which would permit a diagnosis on the basis of etiology. Our analysis of autopsied material available in the Boston City Hospital indicates that the disease is relatively common in early childhood, in pregnancy and again in old age. In infancy and childhood congenital malformations of the kidney and of the urinary tract predispose to the disease.

On postmortem examination the kidneys are usually enlarged and may show small abscesses beneath the capsule. On section, yellow streaks extending from the pelvis to the cortex are evident. The pelvis are reddened, may or may not be dilated, and often are covered with an inflammatory exudate. Microscopically, the tubules contain pus and there is an infiltration of leukocytes in the intertubular connective tissue. Such infiltration is also found in the periglomerular lymphatics and, at times, in the glomerulus (Fig 1), as described by



FIG 1 ACUTE PYELONEPHRITIS PERIGLOMERULAR LYMPHATIC FILLED WITH FIBRIN AND LEUKOCYTES WITH EXTENSION OF THE PROCESS INTO THE CAPSULAR SPACE. $\times 300$

Kimmelstiel and Wilson (20). In addition, multiple abscesses are scattered through both cortex and medulla. Bacteria may be present in the tubules and in the interstitial tissue (Fig 2) as well as in the perivascular lymphatics (Fig 3). At times there may be acute involvement of both arterioles and venules with fibrin formations in the wall and with thrombosis, partial or complete, of the lumen (Figs 4 and 5). Degenerative vascular changes as a result of the infection, however, do not occur. The pelvis shows evidence of acute inflammation often with necrosis and disappearance of the lining epithelium.

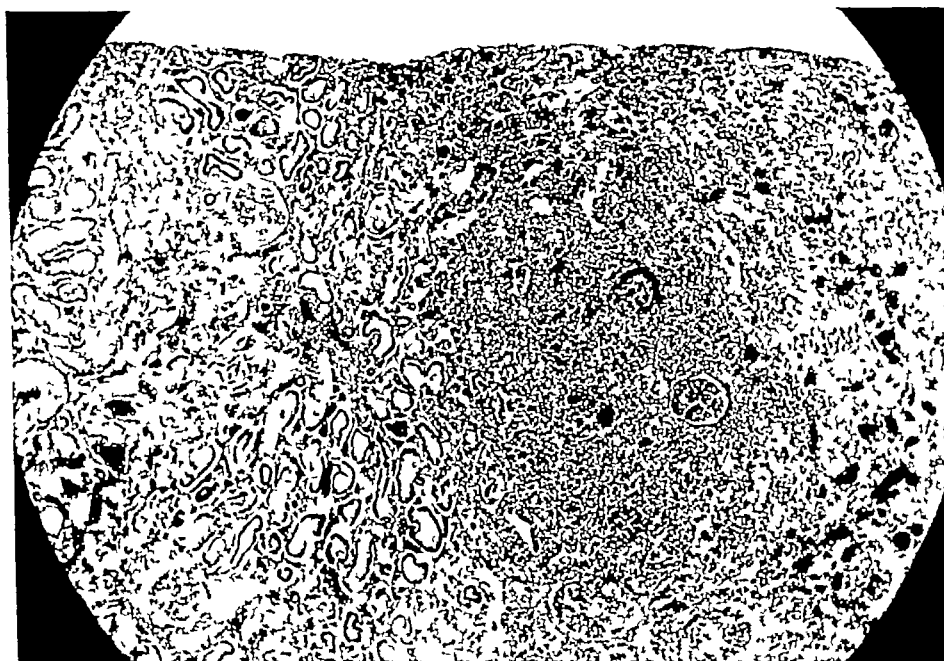


FIG 2 ACUTE PYELONEPHRITIS ABSCESS IN CORTEX $\times 65$

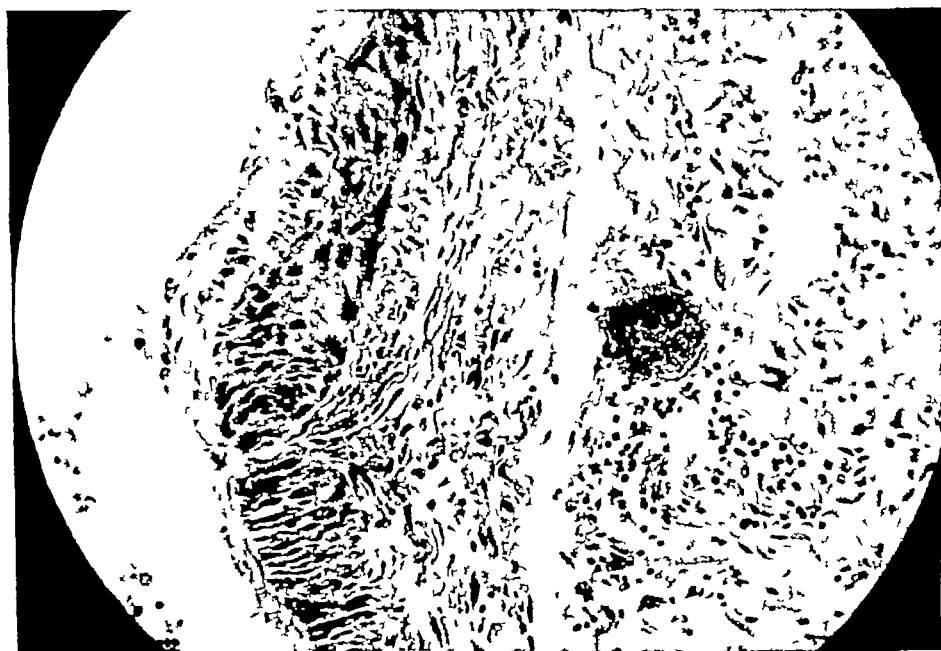


FIG 3 ACUTE PYELONEPHRITIS PERIVASCULAR LYMPHATIC CONTAINING BACTERIA $\times 300$

In all cases of acute pyelonephritis the parenchymatous involvement was essentially identical, irrespective of the type and origin of the infection. With one possible exception, in all instances diagnosed clinically as pyelitis in which the renal pelvis was involved there was also involvement of the parenchyma. The extent of suppuration in the interstitial tissues and within the nephron, respectively, varied considerably. In some instances extensive suppuration was located

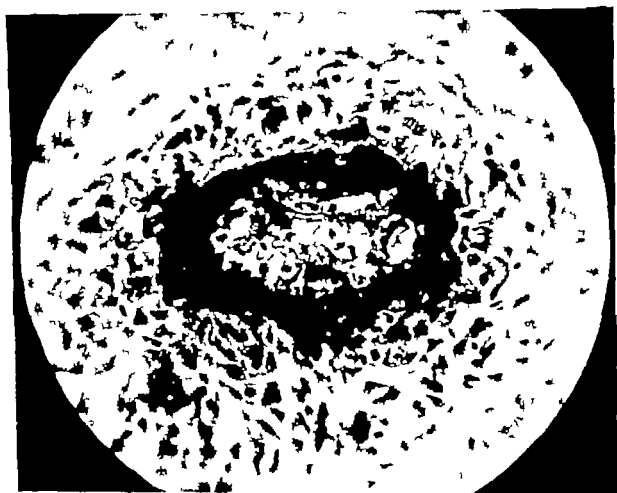


FIG. 4 ACUTE PYELONEPHRITIS. ARTERIOLE WITH FIBRIN IN ITS WALL AND LUMEN INFILTRATED WITH MONONUCLEAR CELLS. $\times 500$

almost entirely in the interstitial tissue. On the other hand, instances with much involvement of the tubules without infection in the interstitial tissue were rare. Acute pyelonephritis is primarily an inflammatory disease of the interstitial tissues. Involvement of the interstitial tissue without invasion of the nephrons accounts for cases which present all the systemic and local manifestations of pyelonephritis but in which the urinary findings are essentially normal. If in such cases pus eventually appears in the urine, this is more apt to

be the result of entrance of the purulent process from the interstitial tissue into the tubules than, as is often claimed, of the opening up of an infected "sealed" pelvis or ureter

We selected 15 patients with acute pyelonephritis for special study. Nine of these were females and 6 were males. The ages of the group varied widely. 4 were infants below the age of 6 months, 2 were children, 5 were young or middle-aged adults and 4 were elderly persons between the ages of 55 and 73. In the infants and the children the

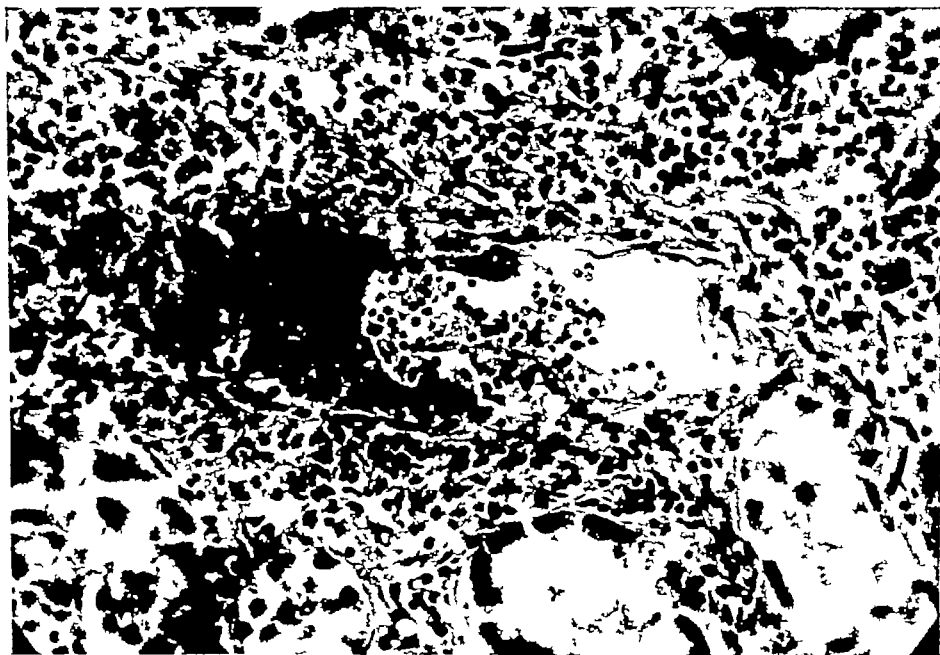


FIG. 5. HEALED, RECURRENT ACUTE PYELONEPHRITIS. SMALL VEIN CONTAINING A THROMBUS. INFILTRATION OF VESSEL WALL AND SURROUNDING TISSUE WITH LEUKOCYTES. $\times 350$

clinical course suggested a hematogenous origin of the disease. In some of the elderly patients the disease might have been due to ascending infection as a result of obstruction by an enlarged prostate or by neoplastic disease. The mode of origin and spread of the renal infection, however, was usually not clear. In all but 2 cases the infection was rather widespread and involved the parenchyma as well as the pelvis. Only 1 case showed elevation of the arterial pressure, and the clinical and histologic evidence indicated that this was in-

dependent of the acute pyelonephritis. None of the patients died of acute pyelonephritis. The disease was either an accidental finding or a secondary complication.

Below we have summarized a few cases of acute pyelonephritis with instructive features.

Case 1 The early stage of pyelonephritis was studied in a 27-year-old woman who had an indefinite history of recent pyelitis. She entered the hospital with a full term pregnancy. The blood pressure was normal. The urine showed an increased number of white blood cells. Following a normal delivery the patient died unexpectedly.

Postmortem examination revealed the following pertinent findings. The uterus was that of recent parturition. The kidneys weighed 375 grams. On section, the cortex averaged 6 mm in thickness. Scattered throughout the parenchyma were small, highly injected areas from which purulent exudate could be expressed. The pelves were moderately dilated and the mucosa was roughened. The ureters were greatly dilated. The right one measured from 1 to 2 cm in diameter, the left was slightly smaller. The bladder was normal. Histologic examination revealed that the infection was limited to the tubules of the papillae and to the pelvis.

This case represents the earliest stage of acute pyelonephritis observed by us.

Case 2 A 4-year-old female child entered the hospital with a fatal attack of cerebrospinal meningitis. Pyelonephritis was not suspected during life. On postmortem examination the following findings were of interest. The pericardium contained 35 cc of slightly greenish fluid. The heart weighed 75 grams and was normal. The cerebral and meningeal vessels were engorged. The cerebrospinal fluid was slightly cloudy. Scattered areas of fibrinous deposits were noted over the surface of the brain. The kidneys weighed 110 grams. The cortex averaged 4.5 mm in thickness. The capsules stripped with ease. The left kidney showed numerous slightly raised, yellowish areas about 1 mm in diameter beneath the capsule. No exudate could be expressed from them. The right ureter was slightly enlarged below the pelvic brim. The bladder was somewhat distended with clear urine. On histologic examination the renal pelvis showed lymphocytic infiltration. The glomeruli were normal in number, but showed periglomerulitis with fibrin. The tubules contained pus but were not dilated. The vessels were normal. The interstitial tissue showed diffuse infiltration by macrophages.

This case is considered an acute hematogenous pyelonephritis (*Ausscheidung Nephritis*)

Case 3 A 58-year-old female patient who had suffered from diabetes mellitus for 10 years had experienced for several months a burning sensation and frequency of urination. There were occasional chills and fever with attacks of pain over both lumbar areas. The cardiovascular system and the arterial pressure were normal. The laboratory findings were characteristic of acute pyelonephritis. Local examination of the bladder indicated a gangrenous cystitis. Because of the presence of a low abdominal tumor, an exploratory laparotomy was performed. The operation revealed a marked degree of edema and some pus of the extraperitoneal tissues above the bladder. The patient died of postoperative complications.

On postmortem examination the kidneys were markedly enlarged, weighing 500 grams. They were soft, flabby and reddish-gray in color. The capsule stripped with ease, leaving a smooth surface on which there were numerous small, yellow areas. The cut surface showed reddish-gray mottling and the markings between the cortex and pyramids were somewhat indistinct. The cortex measured 7 or 8 mm and contained numerous small, yellow nodules. The pelves and calyces were moderately distended. The mucous membrane was grayish-white, mottled with small hemorrhagic areas. The uppermost calyces were greenish-black and necrotic. The ureters were moderately dilated and the walls were soft and friable. The bladder was considerably dilated and the wall was slightly thickened and trabeculated. The mucosa was markedly injected and contained soft ulcerated areas. There was evidence of pelvic peritonitis.

Histologic examination of the kidneys revealed changes indicating gangrene of the papillae. The tubules contained pus. There was diffuse and severe infiltration of the interstitial tissue with lymphocytes and plasma cells. The ureters showed subepithelial congestion with edema and infiltration by lymphocytes and plasma cells. The submucosa of the bladder was congested, edematous and infiltrated with lymphocytes. The subserosal tissue was markedly infiltrated with polymorphonuclear leukocytes.

This case with papillary necrosis is described because it is an example of the type of pyelonephritis occurring in diabetic patients, which was recently discussed by Gunther (21). He has reported 10 cases with necrosis of the renal papillae associated with "ascending" pyelonephritis, 8 of these patients suffered from diabetes.

Case 4 This case, occurring in a 6-month-old female baby, is reported because of the unusual renal changes and because of the difference in the stage of pyelonephritis in the two kidneys. Two weeks before her entrance to the hospital the patient developed an upper respiratory infection which was complicated by a suppurative otitis media. She vomited on several occasions. The physical examination was essentially normal except for an otitis media. Repeated catheterized specimens of urine showed clumps of white blood cells but no increase of albumin. Urine culture showed *B. coli*. The blood Wassermann was negative. The red blood cell count was 4,600,000 and the hemoglobin 75 per cent. The white blood cell count was 19,000. X-ray of the lungs was normal. The temperature fluctuated between 99 and 104° and the pulse between 110 and 130. The patient died of bronchopneumonia.

Postmortem examination revealed the following pertinent findings. The combined weight of the kidneys was 48 grams. The capsule of the right kidney stripped with ease. On the smooth, pinkish-gray renal surface there were several slightly raised, pale yellow areas about 2 mm in diameter. The cortex was 6 mm wide. The pelvis was normal. The ureter was slightly distended, and measured 4 mm in diameter. The capsule of the left kidney stripped with difficulty and the surface was irregular and lobulated. The cortex was between 1 and 2 mm in width. The pelvis was moderately dilated. The ureter was markedly distended, being 7 mm in diameter. The distention reached down to the bladder, but there was no obstruction. The bladder was distended and thin walled.

Histologic examination of the right kidney revealed that it was characteristic of acute pyelonephritis without vascular changes. The left kidney, on the other hand, was affected by changes characteristic of chronic pyelonephritis. In addition, not only were the interstitial tissue and the tubules more affected than those of the right kidney, but the arterioles showed a pronounced degree of hyperplastic arteriosclerosis. The glomeruli of the left kidney were considerably reduced in number.

In this 6 month old baby one kidney was affected by chronic pyelonephritis associated with diminution in size, decrease in the number of glomeruli and secondary vascular changes. The finding of hyperplastic arteriosclerosis in this case is of special significance as it indicates that such vascular changes in the kidney may develop within 6 months, if we assume that the onset of pyelonephritis was not intrauterine. In discussion of the time element of hyperplastic

arteriosclerosis in the lungs, we have concluded that in this organ the vascular changes can occur as early as 2 months (28)

Chronic pyelonephritis

As pointed out by Goppert, Thiemich and others, there are persons in whom pyuria and bacteriuria persist for many years following the initial attack of pyelitis. The clinical manifestations in this group, such as fever, pain, dysuria, anemia and renal failure, depend on the virulence and the extent of the renal infection, as well as on the type of lesions of the urinary tract. In one group in which the condition has persisted for years or even for decades the only systemic manifestations may be anorexia, pallor, lack of energy with obscure fever, and abdominal pain, occurring at varying intervals and lasting for but a few days. There may be a history of passing cloudy urine from time to time for many years. In contrast to the usual cases, in this latter group there may be only a few pus cells in the urine, and at times the diagnosis can be made only with the aid of cultures of the urine which always, or from time to time, are positive. The urine is often alkaline and remains so even after the administration of the usual doses of acid-producing substances. In chronic pyelonephritis, arterial hypertension frequently develops. In these cases the peripheral arteries often become slightly thickened, but the heart is usually not appreciably enlarged. Red blood cells are often found in the urine, and even transient frank hematuria, as a result of rupture of minute vessels, can develop in advanced cases. The face of a patient with chronic pyelonephritis may be slightly puffy and pale, but there is seldom generalized edema.

Cystoscopic and pyelographic examinations of the urinary tract often reveal an inflamed bladder and dilated or constricted ureters and pelvis. On the x-ray plate one sees finger-like projections originating in the calyces, which invade the renal parenchyma.

The extent of abnormality in the urinary findings and the degree of impairment of renal function depend on the nature of the infection and the extent of parenchymatous damage. The concentration and the dilution capacities of the kidney are frequently impaired. Similarly the urea clearance and, subsequently, the phenolphthalein tests indicate renal damage. The rate of progression of the functional

damage varies considerably. The impaired renal function and nitrogen retention often show a considerable degree of fluctuation in accordance with variations in the intensity of suppuration. Frequently moderate nitrogenous retention is present for many years. There is no other type of nephropathy in which a similar degree of fluctuation in renal function occurs as frequently as in chronic pyelo-nephritis. We have observed a few patients with uremia associated with coma and pericarditis in whom following recovery from the uremia the renal function was adequate for several years. Hence the prognosis in cases with chronic pyelonephritis is often difficult. Death is caused by uremia and, more rarely, by complications of arterial hypertension.

In spite of the frequent occurrence of hypertension in these cases, in contrast to those with benign and malignant nephrosclerosis, cerebrovascular accidents, coronary disease and thrombosis did not occur in the series studied. Postmortem examination as a rule also failed to reveal evidence of coronary arteriosclerosis.

On postmortem examination the kidneys may be either enlarged, normal or reduced in size. The larger kidneys are seen especially in association with hydronephrosis. The kidney surface is markedly irregular with areas of destruction and scar formation, such scarred areas being U shaped in contrast to the V shape of vascular scars. In addition, there may be nodular areas representing foci of compensatory dilatation of the tubules. The cut surface reveals scarring with marked narrowing of the cortex in such areas. Grossly, abscesses may be visible, but often the activity of the process can be recognized only microscopically. The walls of the pelvis are thickened, and are often reddened and covered with exudate. The capsule is adherent, stripping from the kidney with difficulty and tearing away tissue with it.

Microscopically the scarred areas contain tubules filled with so called colloid casts and lined with atrophic, flattened epithelium (Fig 6). The glomeruli show concentric pericapsular fibrosis (Fig 7). The glomerular tufts exhibit degrees of sclerosis varying from slight to complete. The vessels show changes to be described later. The interstitial tissue is increased in amount and is infiltrated with lymphocytes and plasma cells, and, if the process is still active in such

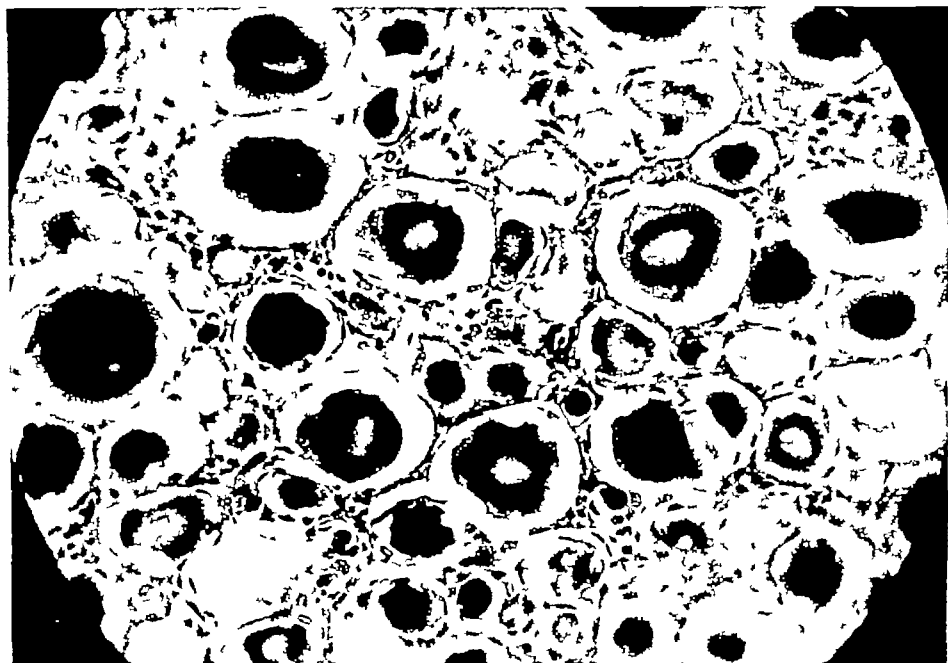


FIG 6 HEALED PYELONEPHRITIS TUBULES LINED WITH FLATTENED EPITHELIUM AND CONTAINING COLLOID CASTS $\times 300$

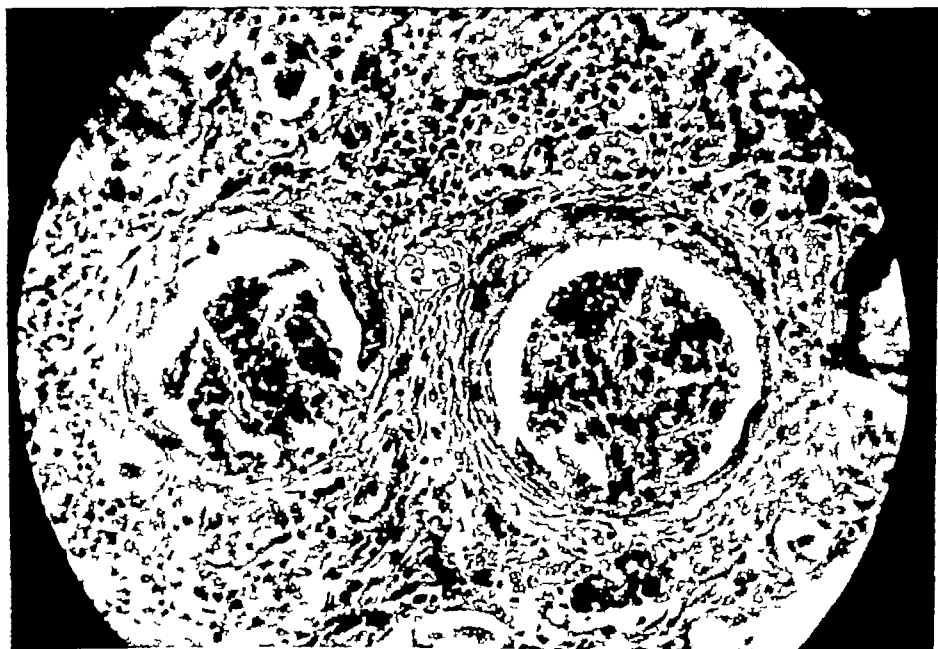


FIG 7 CHRONIC PYELONEPHRITIS PERIGLOMERULAR FIBROSIS $\times 280$

regions, with polymorphonuclear leukocytes. The nonscarred portions may be essentially normal or may show compensatory dilatation of the tubules. If renal failure was present during life the glomeruli in the scarred and the nonscarred areas usually show varying degrees of glomerulitis (22) (Fig 8), depending both on the degree of the failure and on the severity of the vascular changes. Kimmelstiel and Wilson (22) have applied the term "alterative glomerulitis" to cer-

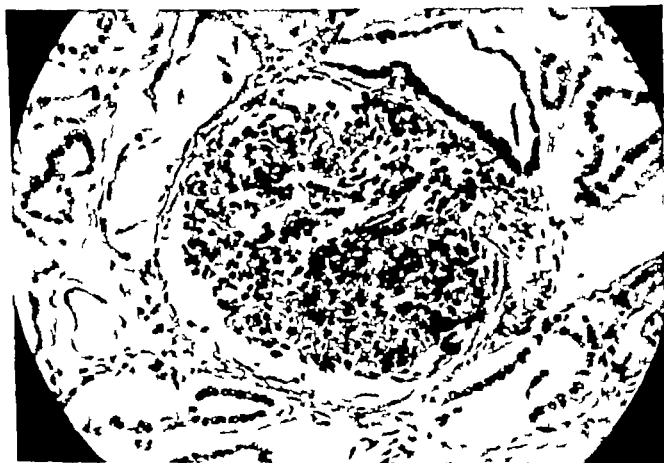


FIG 8 CHRONIC PYELONEPHRITIS, DEATH FROM UREMIA. ALTERATIVE GLOMERULITIS
× 300

tain types of such glomerular lesions. The active pyelonephritic process is recognized by the presence of tubules filled with pus, of polymorphonuclear leukocytes in the interstitial tissue and often of abscess formation. The wall of the pelvis is thickened owing to increased connective tissue which is markedly infiltrated with lymphocytes, plasma cells and polymorphonuclear leukocytes. In addition there may be newly formed lymphoid nodules with active germinal centers (Fig 9). The pelvic epithelium may be covered with an exudate of fibrin and leukocytes or may be absent as a result of erosion

or ulceration. In some instances the pelvis and papillae may be gangrenous. The renal capsule is often thickened and infiltrated with lymphocytes and plasma cells.

In connection with this group of chronic pyelonephritis, cases of so-called chronic interstitial nephritis must be mentioned. Such cases are at times associated with renal dwarfism. In the opinion of Fahr and of others, including ourselves, this type of lesion represents



FIG 9 CHRONIC PYELONEPHRITIS. WALL OF PELVIS SHOWING CELLULAR INFILTRATION AND PRESENCE OF LYMPHOID FOLLICLE IN WHICH HISTIOCYTIC ACTIVITY IS EVIDENT. $\times 140$

chronic or healed pyelonephritis. Microscopically chronic interstitial nephritis differs from the common type of pyelonephritis by the absence of colloid casts and the greater increase in interstitial tissue. The tubules are either atrophic or dilated and, if the process is still active, contain pus. The character of the infiltration and the glomerular changes in general are similar to those described above.

We have made a detailed study of 17 patients with chronic pyelonephritis. The ages of these patients varied between 10 and 69

years, 10 were adults below the age of 40. Nine were males and 8 females. In the majority of cases, history of urinary infection dated back for several years. With the exception of 3 cases, death was due to uremia, high blood pressure or heart failure, singly or in combination. A severe degree of hypertension was present in 8 instances. In 2 cases there was obstruction of the prostate or of the ureter.

The following case reports are examples of chronic pyelonephritis as well as of healed and recurrent pyelonephritis.

Case 5 A 10-year-old girl entered the hospital with ascites and dyspnea. The ascites developed 2 years previously, and at that time a large spleen was found. Physical examination confirmed these findings and in addition revealed tenderness of the abdomen. The heart sounds were of poor quality. The arterial pressure was normal. The urine contained a trace of albumin and a large number of white blood cells, but no casts. The patient developed a high fever, sank into coma and died.

Postmortem examination revealed generalized peritonitis of pneumococcal origin. The spleen was greatly enlarged (860 grams). Both kidneys were enlarged, the right weighing 200 grams and the left 160 grams. The capsule of the right kidney was firmly adherent over the upper pole and tore the kidney substance when removal was attempted. The lower pole was irregular, soft, and deeply scarred and worm-eaten in appearance. Cut surface revealed a markedly dilated pelvis containing a rough, hard, flattened triangular calculus. The left kidney was normal in appearance except for the cortex, which was pale. The mucosa of the bladder was roughened and injected.

Histologic examination revealed that the left kidney was normal. The pelvis of the right kidney showed chronic inflammation. The glomeruli were considerably decreased in number within the pyelonephritic scars, but were otherwise normal. The tubules contained a small amount of pus. The interstitial tissue showed a marked degree of chronic inflammation. The arteries showed moderate thickening and productive endarteritis, and the arterioles only a slight degree of hyperplastic arteriosclerosis in the scars. Elsewhere they were normal.

This case is of interest because it shows an early stage of chronic unilateral pyelonephritis discovered accidentally in a 10-year-old girl who died from peritonitis.

Case 6 This 40-year-old, colored female patient was observed in the Outpatient Department on several occasions between 1932 and 1934. Her

chief complaint at that time was frequency and an occasional burning sensation on urination. On several occasions her urine was bloody. During the period of observation in the Outpatient Department the findings were unessential except for the presence of clumps of white blood cells in the urine. The blood pressure ranged around 160/110 in 1932 and 180/120 in 1934. Pyelographic studies revealed marked dilatation of the right renal pelvis and calyces. The upper third of the right ureter was dilated, while the lower third was contracted. The left ureter was irregular, tortuous and dilated. Cystoscopic examination revealed edema with swelling of both ureteral orifices, particularly over the right side. Specimens of urine obtained from the bladder and from each ureter contained clumps of white blood cells.

In 1935 the patient was admitted to the Surgical Service because of cellulitis of the leg. There were no other complaints. At that time an increased number of white blood cells was again noted and, for the first time, a trace of albumin was found in the urine. In October, 1936 she reentered the hospital because of metrorrhagia. There were no cardiorenal symptoms. Physical examination revealed, however, slight cardiac enlargement and an accentuated aortic second sound. The urine contained a trace of albumin and was loaded with white and red blood cells.

In December, 1936 the patient reentered the hospital complaining of cough of 3 weeks' duration, and of vomiting and dysuria. The heart was enlarged slightly, the aortic second sound was accentuated. The lungs were clear. Numerous measurements of the arterial pressure indicated a level of 270/140 to 280/160. On repeated examinations the urine contained from a slight to a heavy trace of albumin. One specimen contained gross blood. The specimens were "packed" with white blood cells (18 to 20 per high power field). There were no casts, and red blood cells, if present at all, varied from 2 to 4 per high power field. The concentration-dilution test revealed a specific gravity ranging from 1.007 to 1.010. The red blood cell count varied from 2,800,000 to 3,700,000, the hemoglobin from 38 to 43 per cent. The white blood cell count was 7,800. The blood Wassermann and Hinton tests were negative. The non-protein nitrogen was 51 mg per 100 cc on entrance, but in the course of a month gradually rose to 200 mg. X-ray of the chest revealed enlargement of the heart, mainly in the region of the left ventricle. The lung fields were clear. The electrocardiogram revealed left ventricular preponderance. The temperature during the last admission to the hospital varied between 98.8 and 100.8°F. The patient gradually sank into coma and died. The diagnoses were chronic pyelonephritis and "malignant" hypertension.

Postmortem examination revealed the following positive findings. The heart weighed 480 grams, there was hypertrophy of the left ventricle. The combined weight of the kidneys was 210 grams. The capsule of the right kidney stripped with difficulty, tearing away small shreds of cortex. The surface was dark red in color with small, pale nodules from 0.1 to 0.2 cm in diameter. The calyces were markedly dilated, with corresponding decrease in the size of the pyramids. The cortex was narrow. A few small, flame shaped hemorrhages were present in the pelvic epithelium.



FIG 10 CHRONIC PYELONEPHRITIS. WALL OF PELVIS. INCREASED CONNECTIVE TISSUE AND INFILTRATION WITH LYMPHOCYTES AND PLASMA CELLS. $\times 140$

The dilated pelvis continued into a widened ureter for a length of 2 cm. Below this level the ureter was normal. The capsule of the left kidney stripped with difficulty, presenting an irregular, nodular surface similar to that of the right kidney. The cortex was narrow, measuring from 0.3 to 0.5 cm. The fibrous tissue of the parenchyma was increased. Small hemorrhages were present over the surface of the pelvis, but the shape of the pelvis and ureter was normal. The mucosa of the bladder above the trigone was covered with hemorrhages.

Histologic examination of the kidney revealed the following. The pelvis

showed chronic diffuse infiltration (Fig 10) The glomeruli showed alterative glomerulitis with here and there hemorrhages into the glomeruli The glomeruli were reduced in number The tubules were markedly dilated, many of them were atrophic and contained pus The interstitial tissue was infiltrated with lymphocytes The larger arteries showed a pronounced degree of productive endarteritis, the intimal connective tissue staining blue with the phloxin methylene blue stain (Fig 11) There was a marked degree of hyperplastic arteriosclerosis and necrotizing arteriolitis A few of the arterioles showed granulomatous reactions

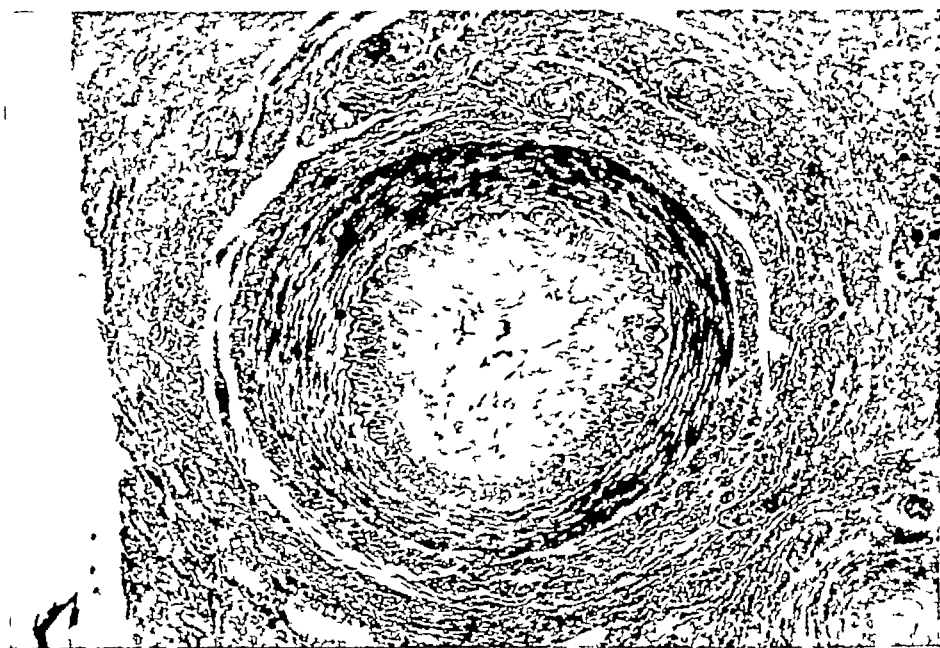


FIG 11 CHRONIC PYELONEPHRITIS PRODUCTIVE ENDARTERITIS THICKENED INTIMA
COMPOSED OF RETICULAR CONNECTIVE TISSUE $\times 100$

In this case pyelonephritis persisted over a period of 5 years During this time the arterial hypertension became progressively severe, ending in a "malignant" phase

Case 7 This 37-year-old married woman was first seen in 1928 in the prenatal clinic She gave a history of "kidney trouble" during previous pregnancies, which had ended in miscarriages At that time the heart was normal The urine contained large traces of albumin and there were varying numbers of white blood cells in the sediment The blood pressure

was 130 to 140 systolic and 90 diastolic. In 1931 the patient complained of nervousness and the blood pressure was found to be 230/130 mm Hg. In 1933 she developed headaches and there was decreased vision. At that time there was puffiness of the eyelids. The discs of the eyegrounds were blurred with patches of exudate and the arteries over the retina were tortuous. The heart was enlarged and the peripheral vessels were tortuous. The blood pressure was 255/143. The urine contained traces of albumin and the sediment, a few to many white blood cells and occasional red blood cells. The non protein nitrogen of the blood was 100 mg. The results of phenolsulphonphthalein tests ranged from 5 to 15 per cent in 2 hours.

In December, 1933 the patient returned to the hospital complaining of nervousness, easy fatigability, increased frequency of urination and urgency. There was some dyspnea and itching of the skin. While in the hospital the patient had a short generalized convulsion. Physical findings were essentially the same as before. The arterial pressure was 190/110. The urea clearance test was 7 per cent. The non protein nitrogen dropped from 200 to 67 mg during her stay in the hospital and her general condition improved.

In May, 1934 the patient again entered the hospital with swelling of the abdomen and of the ankles. The eyegrounds showed a severe degree of neuroretinitis. The heart was enlarged (11.5 cm). The arterial pressure was 240/130. The urine contained albumin and white blood cells. The hemoglobin was 48 per cent and the red blood cell count 2,600,000. The non protein nitrogen was 113 mg and the carbon dioxide combining power 41 volumes per cent. The spinal fluid pressure was 280 mm H₂O. Nine hundred cc of fluid were removed by thoracentesis.

In August, 1934 the patient entered the hospital the last time because of frank hemoptysis. She complained also of palpitation of the heart, disturbed vision and vomiting. Physical findings were essentially unchanged except for a pericardial friction rub. The blood pressure varied between 220 and 240 systolic and between 110 and 140 diastolic. In some specimens of urine there were few, in others many white blood cells, but there were no casts. The hemoglobin ranged from 38 to 40 per cent, the red blood cell count from 1,900,000 to 2,600,000 and the white blood cell count from 6,300 to 11,700. The non protein nitrogen was between 140 and 200. The carbon dioxide combining power was between 8 and 15 volumes per cent. A ray examination of the lungs showed congestive changes. Urine culture contained *B. coli communis*, *staphylococcus albus* and *streptococcus viridans*. The patient became comatose and died on October 11, 1934.

Postmortem examination revealed the following essential findings. The heart weighed 520 grams, with predominating left ventricular hypertrophy. The combined weight of the kidneys was 64 grams. The capsule was firmly adherent. The pale surface was coarsely as well as finely irregular, with small and large depressed areas. The cortex was 0.2 mm in width. The vessels were prominent. Both ureters were dilated, but there was no obstruction. The bladder was normal.

Microscopic examination revealed evidence of chronic pyelonephritis. There were pronounced inflammatory changes in the pelvis. There was acute and chronic alternative glomerulitis and, in addition, many of the glomeruli were sclerosed. The tubules were dilated and contained pus. The interstitial tissue was markedly increased and was infiltrated with lymphocytes and plasma cells. The larger arteries showed productive endarteritis and the arterioles showed hyperplastic arteriosclerosis and necrotizing arteriolitis. The renal capsules were thickened and infiltrated with lymphocytes.

Case 8 A 46-year-old married female entered the hospital in July, 1934 because of frontal headaches and blurred vision of 3 days' duration. Ever since she could remember she had had frequency with nocturia four to five times. Physical examination revealed slight tortuosity of the arteries, but otherwise normal eyegrounds. The heart was slightly enlarged and there was an accelerated aortic second sound. The right kidney was palpable and slightly tender. The arterial pressure dropped from 260/160 to 170/120. The urine at first contained albumin and slightly increased numbers of white blood cells, but subsequent specimens were entirely normal. The phenolsulphonphthalein test was 40 per cent in 2 hours. The concentration-dilution test varied between 1.006 and 1.012. The non-protein nitrogen was 34 and 36 mg per 100 cc of blood. The red blood cell count was 3,000,000 and 3,200,000, and the hemoglobin 50 and 62 per cent. The spinal fluid pressure was 480 and the Pandy test 2 plus. A pyelogram revealed marked deformity of the left renal pelvis. The right pelvis, calyces and upper part of the ureter were deformed. X-rays of the heart and lungs were normal. A diagnosis of chronic left pyelonephritis with abscess was made and nephrectomy was performed on August 29, 1934.

The capsule of the kidney stripped with ease, revealing a pale, brownish surface from which projected yellowish elevations. On section the cortex was found to measure 0.3 by 0.5 cm in width. There were many abscesses in the cortical region, varying from 0.1 to 0.3 cm in diameter. The pelvis and calyces were markedly dilated. The mucosa of the pelvis was thickened, whitish in color and smooth.

Microscopic examination showed healing pyelonephritis with a considerable amount of pus in the tubules, but no colloid casts. Abscesses were present and showed signs of organization. The glomeruli were normal. The arteries showed a slight degree of productive endarteritis, and the arterioles a slight degree of hyperplastic arteriosclerosis (Fig 12). The interstitial tissue was acutely inflamed and was infiltrated with polymorphonuclear leukocytes and with lymphocytes.

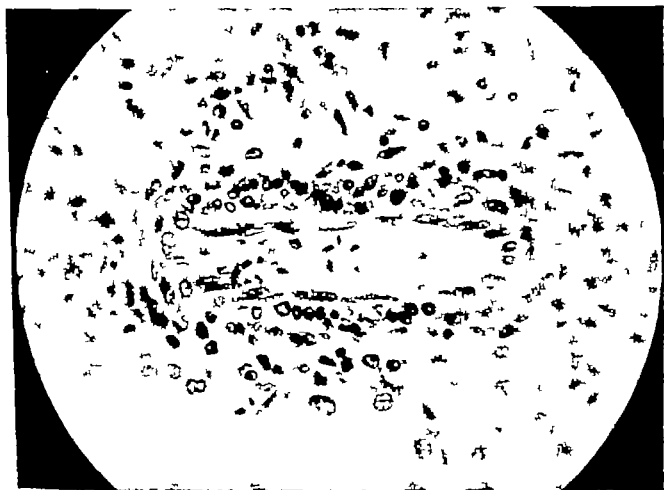


FIG 12 CASE 8 ARTERIOLE FROM KIDNEY REMOVED SURGICALLY. ESSENTIALLY NEGATIVE EXCEPT FOR SLIGHT INFILTRATION OF CELLS IN ITS WALL AND SURROUNDING TISSUE. $\times 550$

Following discharge from the hospital in November, 1934, the patient resumed work. In July, 1935 she developed nausea, epigastric fullness and orthopnea. Physical examination revealed marked neuroretinitis with exudates, hemorrhages and papilledema. The blood pressure was 245/145. The rest of the findings were unessential. Specimens of urine obtained from the right ureter contained clumps of white blood cells. A pyelogram revealed dilatation of the upper part of the right ureter (Fig 13). The phenolsulphonphthalein test showed 5 per cent excretion in 2 hours. The

non-protein nitrogen rose from 67 to 200 mg per 100 cc The patient fell into coma and died in August, 1935 (Chart 1)

Postmortem examination revealed the following pertinent findings The heart weighed 465 grams and there was a moderate degree of hyper-



FIG 13 CASE 8 PYELOGRAM OF RIGHT KIDNEY

trophy of the left ventricle The right kidney weighed 240 grams (moderately enlarged) The capsule stripped with slight difficulty, revealing a pale, reddish-gray surface studded throughout with small, petechial hemorrhages At the upper pole there were miliary abscesses which, on section, were seen to extend into the cortex and the medulla On cut section the

cortex, which was 1.1 cm in thickness, could scarcely be differentiated from the medulla. The pelvis and calyces were markedly dilated and the walls showed areas of hemorrhage. The papillae were markedly reddened. The ureter was dilated to a circumference of 2 cm to a point about halfway down its length, where it rather suddenly became reduced to a circumfer

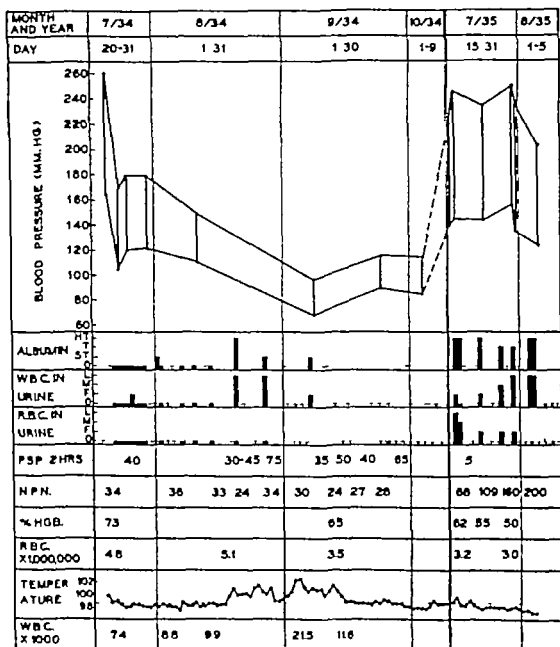


CHART 1 FEATURES OF CLINICAL COURSE IN CASE 8

ence of 1.1 cm. From here to its entrance to the bladder it was of normal size. The mucosa of the bladder was markedly injected.

Microscopic examination of the right kidney revealed chronic pyelonephritis. The pelvis showed chronic inflammation. The glomeruli were reduced in number and showed pronounced necrosis and alternative glomerulitis. The tubules were dilated, in the scars they were plugged with casts.

and, here and there, contained pus. The interstitial tissue was infiltrated with polymorphonuclear leukocytes and with lymphocytes. A pronounced degree of productive endarteritis, hyperplastic arteriosclerosis and necrosis of the arterioles was present (Fig. 14).

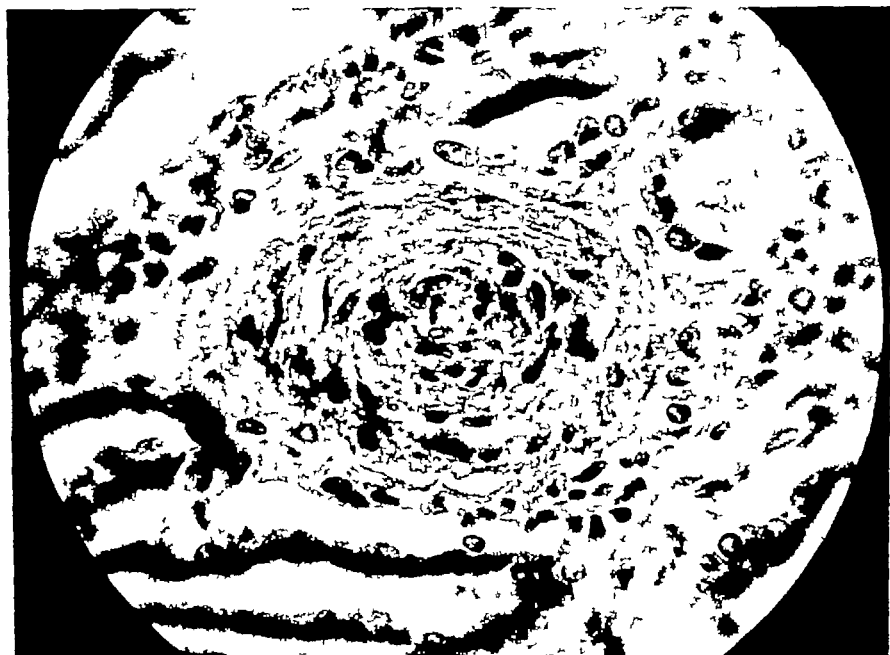


FIG. 14 CASE 8 ARTERIOLE FROM KIDNEY OBTAINED AT AUTOPSY
HYPERPLASTIC ARTERIOLOSCLEROSIS $\times 550$

This case is of especial interest because of differences in the degree of vascular changes in the kidney removed surgically 1 year before death, and in the right kidney observed postmortem.

Case 9 This 23-year-old married female's difficulties started in 1931 with an attack of acute pyelonephritis during pregnancy. She had chills, fever, dysuria and frequency. The blood pressure and the urine were normal in the early stage of pregnancy, but 2 weeks before term edema developed and the urine contained a trace of albumin and a few white blood cells. The blood pressure was 142/108. The patient was admitted to the hospital in January, 1932 with slight dyspnea on exertion and edema of the extremities. The arterial pressure was 164/126. Forceps were used for delivery because of the presence of "toxemia" of pregnancy. Eight days after delivery the arterial pressure was 128/76. A catheterized

specimen of urine contained a trace of albumin and more than 100 white blood cells per high power field. The non protein nitrogen was 26 mg per 100 cc.

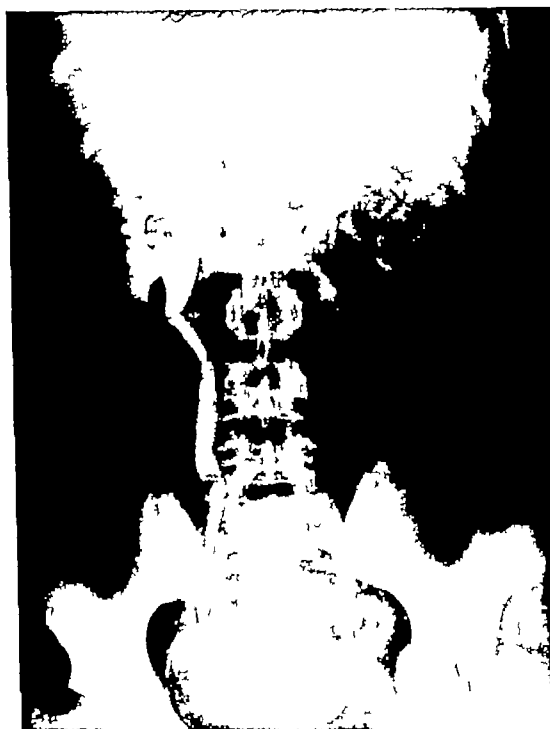


FIG. 15. CASE 9. PYELOGRAM OF RIGHT KIDNEY.

Two months after delivery the patient suffered an attack of right lumbar pain which radiated, as a burning sensation, to the right groin. She had fever and chills, urgency, frequency and vomiting. Thereafter attacks occurred at about monthly intervals and lasted for 5 or 6 days. In January 1935 the patient returned to the Gynecological Service with com-

plaints of dysuria and frequency. Physical examination revealed tenderness over the lumbar areas. Urine culture yielded *B. coli*. Albumin was present and, in some specimens, clumps of white blood cells were observed. The ureter specimens contained a moderately increased number of white



FIG 16 CASE 9 PYELOGRAM OF LEFT KIDNEY

blood cells. On cystoscopic examination the bladder appeared normal. Pyelogram revealed defects of the upper portions of the pelvis and calyces, tortuosity and dilatation of the ureter on the right, and slight dilatation of the calyces on the left (Figs 15 and 16). The temperature ranged from 99 to 100°F. A diagnosis of acute (*B. coli*) pyelonephritis was made.

In May, 1935 the patient returned to the hospital for general examination, without complaints. The essential finding was blurring of the temporal aspects of the optic discs. The heart was not enlarged, but the aortic second sound was ringing. The arterial pressure was elevated to between 180 and 230 systolic and between 110 and 135 diastolic. The urine contained a trace of albumin and in some specimens there was a slightly increased number of white blood cells. In the majority of specimens, however, the sediment was normal. The concentration dilution test showed a fixation of 1 006 to 1 010. The phenolsulphonphthalein test was 35 per cent in 2 hours. Urine culture yielded *B. coli communis*. The blood non-protein nitrogen was 42 mg per 100 cc. The red blood cell count was 4,300,000, the hemoglobin 74 per cent and the white blood cell count from 6,300 to 7,200. Cystoscopic examination revealed some edema of the trigone. A urine specimen obtained from the right ureter contained 3 to 4 white blood cells per high power field. The urine from the left ureter was entirely normal. The pyelogram showed a filling defect of the superior major calyx and some retention of the minor calyces. The patient remained asymptomatic and afebrile during hospitalization.

In August, 1935 the patient returned to the hospital because of blurred vision. For a month she had been unable to read. Attacks of severe headache and vomiting developed. Frequency of urination was present day and night. On physical examination there was puffiness under the eyes. There was papilledema with tortuosity of the veins and white exudates of the eyegrounds. The heart was slightly enlarged. The rate was 140 and regular. There was a blowing systolic murmur over the apex. The arterial pressure usually fluctuated around 250/190, at times it dropped lower. There was tenderness over the left kidney. X-ray examination on admission showed the cardiac diameters to be barely within the limits of normal, but 12 weeks later they were enlarged (Figs 17 and 18). The specific gravity of the urine was between 1 007 and 1 009. There was a trace of albumin and in some of the specimens 20 to 50 white blood cells per high power field. Urine cultures yielded *B. coli communis* and diphtheroid organisms. The phenolsulphonphthalein test on entrance, and also a few days before death, was 10 per cent in 2 hours. The Kahn test of the blood was negative. There was progressive anemia, reaching a level of 2,000,000 to 3,000,000 red blood cells and 44 per cent hemoglobin. The white blood cell count was usually normal, but on two occasions it was 15,000. The non protein nitrogen fluctuated between 60 and 98 mg per 100 cc. The electrocardiogram indicated changes consistent with severe hypertension and "myocardial disease". Examination of the spinal fluid showed a pressure of 300 and increased protein content. On August 16

a cystoscopic examination revealed edema around the trigone. A specimen of urine from the right ureter contained 20 to 30 clumped white blood cells per high power field, a specimen from the left showed no white blood cells. On August 20, however, the ureter specimens were normal. The tempera-

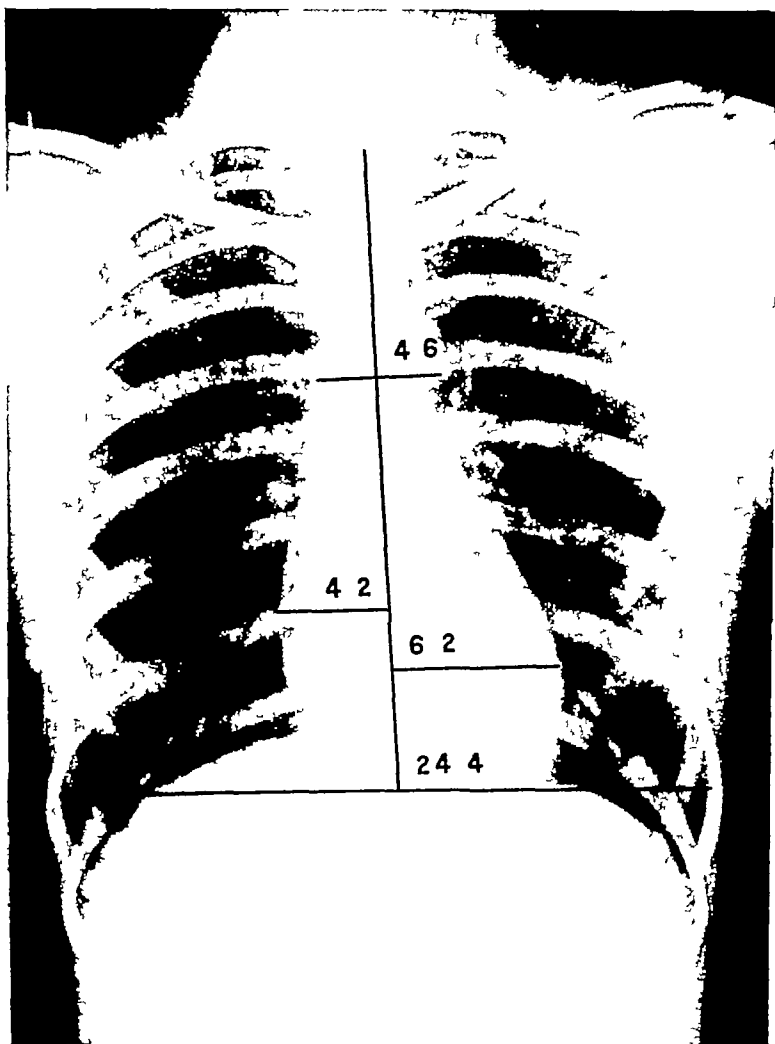


FIG 17 CASE 9 ROENTGENOGRAM OF HEART, MAY 14, 1935

ture was essentially normal. Toward the end of her 6 weeks' stay in the hospital the patient became blind, developed attacks of vomiting and convulsions, lapsed into coma and died (Chart 2).

Postmortem examination was restricted to examination of the kidneys.

The right kidney weighed 55 grams and the left 58 grams. The surface of the right kidney was nodular and irregular, and contained depressed areas (Fig 19). The ureter emerged from the lower pole. The capsule stripped with difficulty and revealed a shriveled, granular surface with

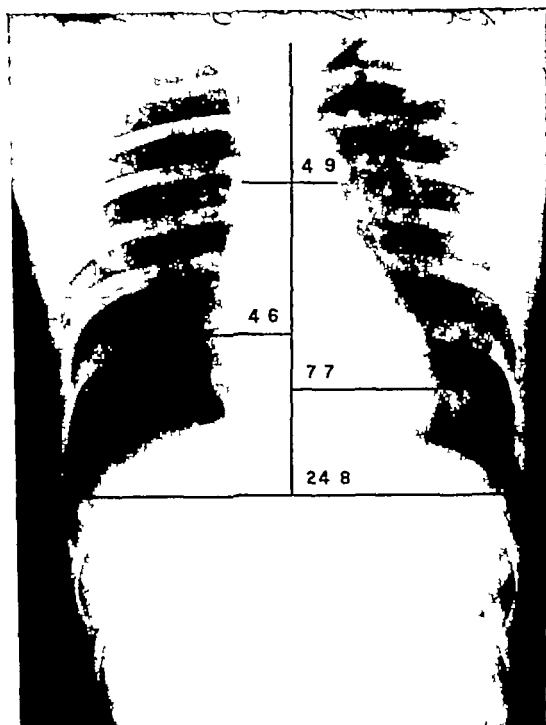


FIG 18 CASE 9 ROENTGENOGRAM OF HEART AUGUST 9 1935

two large raised areas, covered by a finer granular surface. The cut section showed marked irregularity and atrophy of the cortex, which was obliterated in various places and measured only 2 or 3 mm in others (Fig 20). The pyramids were small and distorted, with marked scarring. The

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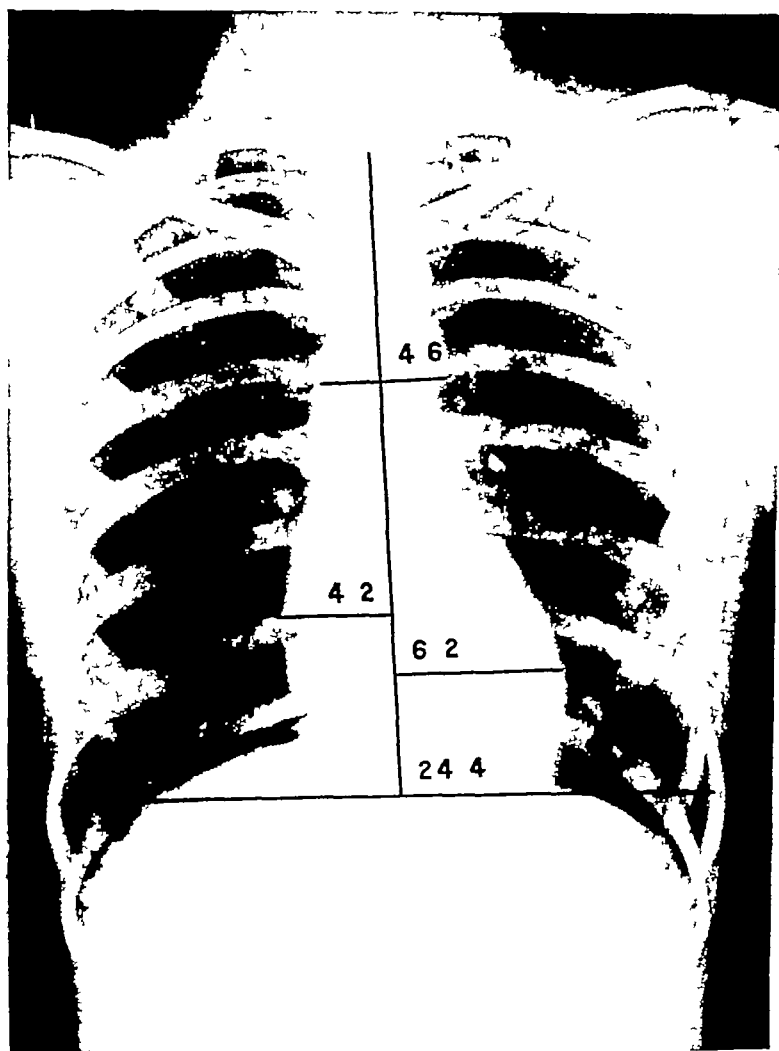


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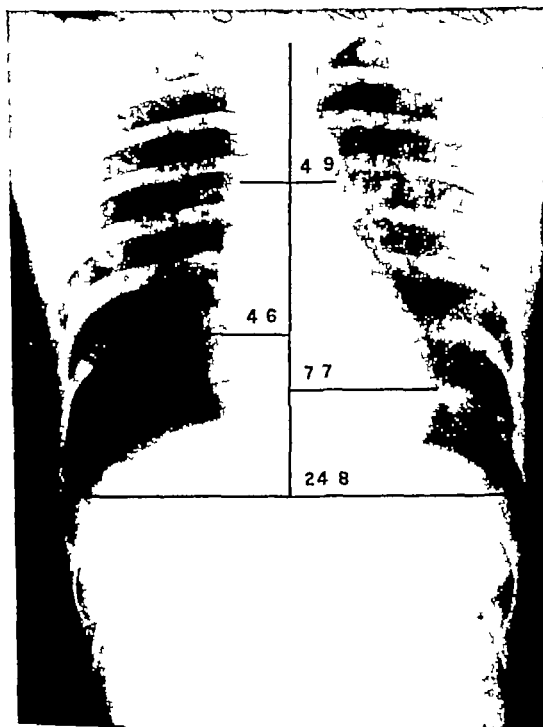


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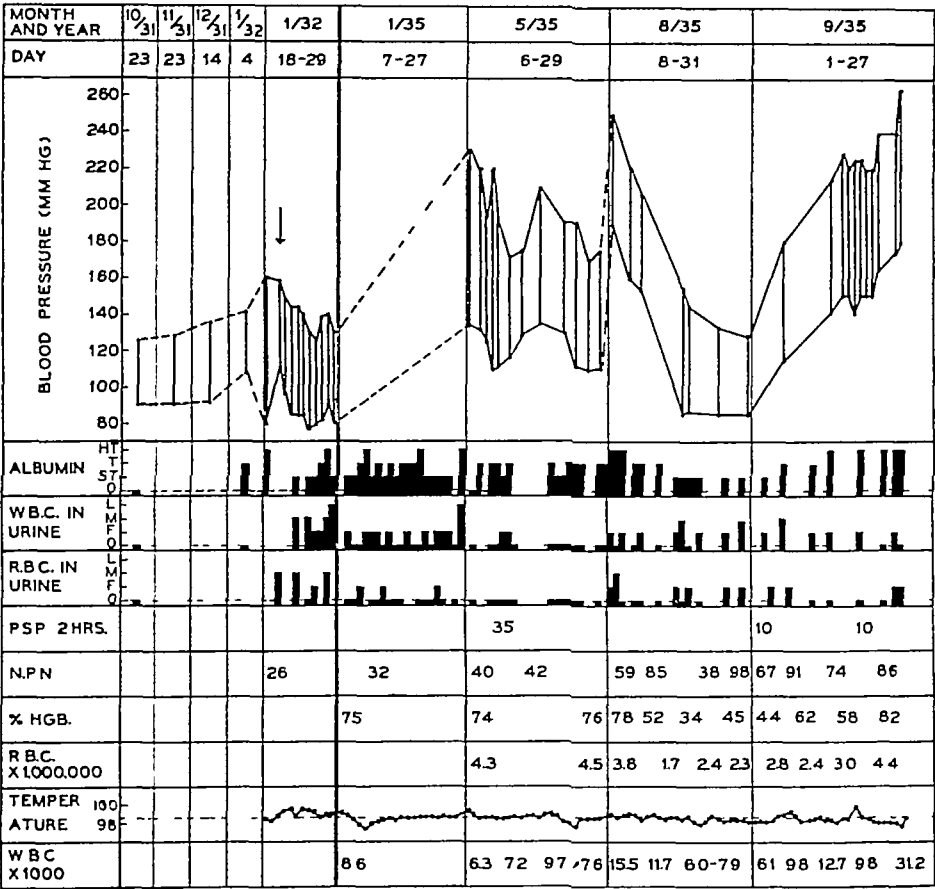


CHART 2 FEATURES OF CLINICAL COURSE IN CASE 9



FIG 19 CASE 9 GROSS APPEARANCE OF KIDNEYS

pelvis was dilated and distorted. The left kidney presented essentially the same picture as the right.

Microscopic examination showed chronic pyelonephritis. The glomeruli showed some necrosis and alterative glomerulitis. There was a pronounced degree of sclerosis over certain areas. The majority of the tubules were plugged with casts, those remaining were dilated. In some areas the tubules contained pus. The interstitial tissue was increased and showed chronic inflammation with a marked degree of infiltration with lymphocytes and with eosinophils. There was a pronounced degree of productive endarteritis and also severe hyperplastic arteriosclerosis. Some arterioles were necrotic and a few showed hyaline degeneration. The vascular changes were particularly pronounced in the pyelonephritic scars.

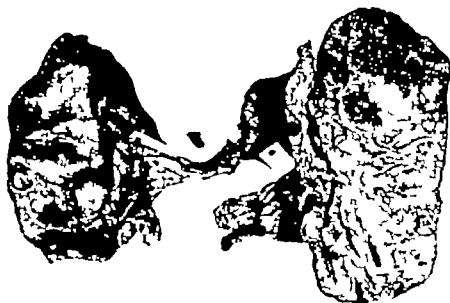


FIG. 20. CASE 9. GROSS APPEARANCE OF CROSS SECTION OF KIDNEYS.

Case 10. An 18-year-old girl entered the hospital complaining of bleeding gums. She had suffered from numerous attacks of sore throat. During the past 4 or 5 years she had suffered from dyspnea on exertion and fatigability. Hemorrhages of the retina and tortuosity of the vessels were present. There was a diffuse apex impulse with a gallop rhythm over the mitral area, where a systolic murmur was heard. The arterial pressure was 220/130. The urine contained a trace of albumin and many free and clumped white blood cells. The specific gravity varied between 1.006 and 1.012. The blood non-protein nitrogen ranged between 171 and 258 mg. The blood Wassermann was negative. The patient died of uremia 2 weeks after admission.

Postmortem examination revealed the following essential findings:

The heart weighed 320 grams and there was slight hypertrophy of the left ventricle. The left kidney weighed 38 grams, and the right 23 grams. The capsule stripped with difficulty, exposing an irregular, pearly white surface. The cortex was so narrow as to be almost unrecognizable, averaging not more than 1 mm in thickness. The pyramids were contracted. The pelvis of the right kidney was thickened and moderately enlarged. The ureters were normal. The mucosa of the bladder, except for small hemorrhages, was normal.

Histologic examination of the kidneys revealed a slight degree of alterative glomerulitis. The tubules were dilated and contained pus. A relatively small number of tubules were occluded with casts. The interstitial tissue was infiltrated diffusely with lymphocytes and with polymorphonuclear leukocytes. There was a slight degree of productive endarteritis and a moderate degree of hyperplastic arteriosclerosis. The histologic diagnosis rested between chronic and recurrent acute pyelonephritis.

Healed pyelonephritis

The clinical diagnosis of healed pyelonephritis offers special difficulty. In the majority of instances this is but the end stage of acute focal pyelonephritis (pyelitis) of short duration. Such small pyelonephritic scars are usually of no clinical significance, as is indicated by the frequency of their "accidental" discovery during routine post-mortem examination. These scars may be compared to the small healed tuberculous lesions found in the lungs. Cases with such localized lesions were not included in the series studied. There are, on the other hand, an appreciable number of patients who, after suffering from chronic or from repeated attacks of acute pyelonephritis, apparently recover, but who, usually after a period of years, develop arterial hypertension, with or without symptomatic renal impairment. In a smaller group renal failure with uremia but without arterial hypertension ultimately develops. For years some of these patients may have slight puffiness of the face, sallow complexions and dry skin. At times they are young persons with retarded physical development. Severe edema without cardiac complication is rare. There is a tendency to a moderate degree of anemia. Impairment of the concentration and dilution capacities of the kidney is frequent.

The urea clearance test is often low, frequently without retention of nitrogenous waste products in the blood. Evidence of urinary infection is lacking. There may be a history of urinary infections and of albuminuria in the past. Increased numbers of white cells may be present in the urine from time to time, but in many instances even repeated counts (Addis) of the white cells fail to reveal abnormal elevation. The pyelogram may show deformities of the pelvis, calyces and ureters, frequently, however, there are no changes, as also indicated by the postmortem examination. Not infrequently the disease remains unrecognized until symptoms of uremia call attention to the rapid approach of the fatal terminal stage.

If the arterial pressure is markedly elevated the usual manifestations and complications of severe hypertension may develop, such as headaches, vertigo, vascular crisis, eyeground changes and elevation in the spinal fluid pressure, often with increased protein content of the spinal fluid. Elevation in the spinal fluid pressure is apt to be associated with albuminuric retinitis, vascular crisis and uremia. Coronary disease or thrombosis did not occur in our group, notwithstanding the severity of the arterial hypertension. Postmortem examination also failed to show a pronounced degree of coronary disease. Similarly, intracerebral hemorrhage did not develop. The cause of death was usually uremia or cerebral crisis, and seldom cardiac failure. The progression of the disease in the healed stage shows great variation. For years the condition of the patient may remain stationary. The development of severe hypertension is, however, usually of grave prognostic significance. Frequently it further accentuates the previously existing renal damage.

As a rule the clinical diagnosis of healed pyelonephritis can be established with only a fair degree of probability. The history of attacks of pyelonephritis and anatomic abnormalities of the urinary tract favor this diagnosis. Toxemia of pregnancy occurs relatively frequently. Absence of a history of glomerulonephritis also represents indirect supporting evidence. Children and, at times, young adults with healed pyelonephritis are underdeveloped and have changes in the bones (renal rickets hyperparathyroidism) or in the distribution of the fat tissue, as well as in the carbohydrate metabolism (diabetes).

(23, 24, 25) In patients with hypertension with good or fair renal function and with inadequate history the diagnosis is particularly difficult and often cannot be established with any degree of certainty

The progression of structural lesions is characterized by the fact that, although the infectious process has healed, the chronic inflammatory tissue reactions often continue, causing progressive damage to the nephrons and to the vessels

Grossly the kidneys are usually reduced in size and show multiple scars in the cortex. Between the scars there are often nodular areas. There is a reduction in the thickness of the cortex and an increase in connective tissue in the scarred regions. The walls of the calyces and pelvis are thickened and may or may not be dilated. In some instances the calyces and pelvis are contracted. The variation in size of the two kidneys, associated with irregular-sized scars, differentiates this type of kidney disease from nephrosclerosis and glomerulonephritis. Occasionally, the appearance of a kidney with multiple healed infarcts resembles that of healed pyelonephritis.

Microscopically, in the scarred areas the tubules are filled with colloid casts, which are indicative of nonfunctioning nephrons. The connective tissue is increased and is infiltrated with lymphocytes and plasma cells. The glomeruli often show a concentric increase in connective tissue of the capsules or may be partially or completely sclerosed. Glomerulitis is present if renal failure existed during life. Changes in the vessels in such scarred areas will be described later. Between scarred and nonfunctioning areas and corresponding to the nodular areas noted grossly there is dilatation of tubules, presumably of a compensatory nature. There is usually a fibrous thickening of the kidney capsule, which in addition is infiltrated with lymphocytes and plasma cells. The wall of the pelvis is thickened owing to an increase in connective tissue and is infiltrated with lymphocytes and plasma cells. In some instances there may be formation of lymphoid nodules with active germinal centers.

While the histologic diagnosis of pyelonephritis in the active stage rarely presents any difficulty, in the healed stage it is often difficult to determine whether one is dealing with a healed pyelonephritis with associated vascular changes or with a primary vascular kidney disease. In making a histologic differential diagnosis between the two con-

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systems were normal. The systolic blood pressure was 110 to 120 and the diastolic 80 to 85. Numerous specimens of urine failed to show abnormal findings. The Kahn test of the blood was negative. The non protein nitrogen was 37 mg per 100 cc.

In 1936 the patient was readmitted with attacks of "renal colic." Fourteen months previous to this admission he first experienced painful and

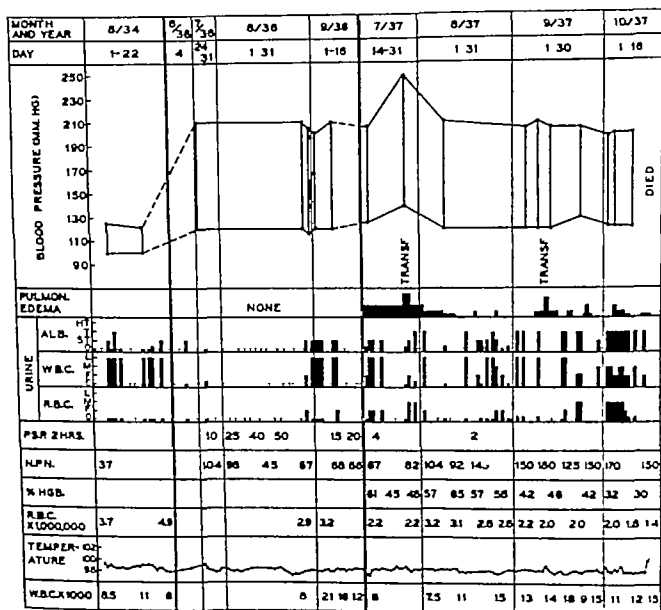


CHART 3 FEATURES OF CLINICAL COURSE IN CASE 12

burning urination. He had chills and fever and passed bloody urine, but recovered from this attack within a few days. Three months later he had a similar attack and at that time a diagnosis of bilateral renal calculi was made. He felt well for about 2 months, he then had recurrence of pain, hematuria and fever. Examination revealed some tenderness over both kidneys and elevated arterial pressure. At this time the non protein nitrogen of the blood was 104 mg and the phenolsulphonphthalein test was

blood non-protein nitrogen varied between 30 and 44 mg per 100 cc. The hemoglobin was 90 per cent and the white blood cell count 14,000 to 15,000. The blood Kahn was negative. Because a brain tumor was suspected by the neurologic consultants, repeated lumbar taps were done. The spinal fluid pressure on these occasions was 450, 380 and 390 mm H₂O, respectively. The abdominal distress became worse and the patient died of circulatory collapse.

Postmortem examination revealed the following essential findings. The heart weighed 230 grams (normal 124 grams). The left ventricular wall was hypertrophied. The serosal surface of most of the ileum was dull and covered with fibrin. The wall was friable and its color was purple and grayish-white. The mucosa was brown in some places and brownish-green in others. There were several ulcerated areas. The left kidney weighed 10 grams, the right 110 grams (normal 95 grams). The surface showed yellowish-white areas. The right cortex was 6 to 8 mm and the left 1 to 1.5 mm in thickness. The pelvis of the left kidney was slightly dilated. The left ureter was normal in size, the right slightly dilated. The renal artery on the left side was small. The bladder was normal.

Microscopic examination of the kidneys revealed the following. The pelvis of the left kidney showed a pronounced degree of chronic inflammation. The tubules were markedly dilated and the majority were filled with colloid casts, no pus was present. Only a few glomeruli were present. The interstitial tissue was increased and showed a moderate degree of lymphocytic infiltration. The larger arteries showed pronounced productive endarteritis, while the arterioles showed advanced hyperplastic arteriosclerosis and some necrotizing arteriolitis. The right kidney showed no evidence of pyelonephritis, but the vascular changes were similar to those in the left kidney, though less severe.

This case is of interest because it shows the association of healed unilateral pyelonephritis in a 12-year-old girl with malignant hypertension and nephrosclerosis. The changes in the right kidney were in a relatively early stage, because death was caused by infarction of the bowels and not by uremia.

Case 12 This 39-year-old male was first admitted to the hospital in 1929 because of acute alcoholism. His blood pressure was normal (110/64). In 1934 he was readmitted, suffering from chronic alcoholism and pellagra. At that time he had had nocturia four to five times, but gave no history of dysuria, hematuria or pyuria. The cardiovascular and genitourinary

elevated areas projecting about 3 mm above the kidney surface. Cut section revealed a light-red cortex which measured approximately 2 mm in depth except where the plateau like islands of hyperplasia made it 5 mm. The pyramids were poorly defined against the light red background.



FIG. 21. CASE 12. PYELOGRAM OF RIGHT KIDNEY.

In the anterior half of the kidney was embedded a dark brown stone. The capsule of the left kidney stripped with ease, revealing a smooth, irregular surface. The cortex measured approximately 3 mm in depth. In the posterior half, at the base of one poorly defined pyramid, was a small, spherical stone. At the inferior pole there was a 'stag horn' stone, measur

10 per cent in 2 hours When the patient was placed on forced fluid intake the non-protein nitrogen fell and the phenolsulphonphthalein test rose to 50 per cent in 2 hours The calcium level on two occasions was normal and the phosphorus slightly elevated X-ray of the long bones revealed a cyst-like structure in the right femur which was thought not to be osteitis fibrosa cystica During his stay in the hospital the patient felt comfortable X-ray revealed slight hypertensive deformity of the heart Other pertinent findings are indicated on Chart 3 Diagnoses of pyelonephritis and renal calculi were made

Following his discharge in September, 1936 the patient felt fairly comfortable until June, 1937, when he developed edema of the ankles, bilateral flank pain radiating to the groin, frequency and nocturia His face began to be puffy in the morning Following a respiratory infection he became dyspneic on exertion He reentered the hospital in July, 1937 with dyspnea and lumbar pain There was mild bilateral papilledema with white scars on the right disc The heart was slightly enlarged and the aortic second sound was accentuated The abdomen was distended with ascites Some of the findings are presented on Chart 3 Urine cultures on several occasions soon after entrance showed *B. coli communis* The Hinton test of the blood was negative The total protein of the blood was 5.7 and 5.5 grams with an albumin-globulin ratio of 1.3 and 1.6, respectively The blood serum calcium was 8.6, 8.2 and 7.2 and the phosphorus 5.4, 7.2 and 7.2 mg per 100 cc, respectively The carbon dioxide combining power of the blood dropped from 30 to 15 volumes per cent X-ray examinations revealed kidney stones (Figs 21 and 22) and a small cyst in the neck of the femur The electrocardiogram showed changes consistent with hypertensive heart disease

The patient was placed on a high carbohydrate, salt-free diet His condition showed considerable fluctuation Three weeks before death a harsh friction rub was heard over the precordium Vomiting and headaches developed He had several attacks of paroxysmal dyspnea with pulmonary edema In October, 1937, the day before his death, he developed a chill and abdominal tenderness His temperature rose to 101.5°F and a blood culture was positive for *Streptococcus hemolyticus*

The essential findings at postmortem examination were as follows The pericardium was thickened and the cavity contained approximately 500 cc of thick, bloody fluid The left ventricle was moderately hypertrophied Acute peritonitis was present The combined weight of the kidneys was 240 grams The capsule of the right kidney stripped with ease, revealing a uniformly granular surface upon which there were flat-topped,

elevated areas projecting about 3 mm above the kidney surface. Cut section revealed a light-red cortex which measured approximately 2 mm in depth except where the plateau like islands of hyperplasia made it 5 mm. The pyramids were poorly defined against the light red background.



FIG. 21. CASE 12. PYELOGRAM OF RIGHT KIDNEY.

In the anterior half of the kidney was embedded a dark brown stone. The capsule of the left kidney stripped with ease, revealing a smooth, irregular surface. The cortex measured approximately 3 mm in depth. In the posterior half, at the base of one poorly defined pyramid, was a small, spherical stone. At the inferior pole there was a "stag horn" stone, measur-

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elevated areas projecting about 3 mm above the kidney surface. Cut section revealed a light red cortex which measured approximately 2 mm in depth except where the plateau like islands of hyperplasia made it 5 mm. The pyramids were poorly defined against the light red background.



FIG 21 CASE 12. PYELOGRAM OF RIGHT KIDNEY

In the anterior half of the kidney was embedded a dark brown stone. The capsule of the left kidney stripped with ease, revealing a smooth, irregular surface. The cortex measured approximately 3 mm in depth. In the posterior half, at the base of one poorly defined pyramid, was a small, spherical stone. At the inferior pole there was a "stag horn" stone, measur-

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elevated areas projecting about 3 mm above the kidney surface. Cut section revealed a light-red cortex which measured approximately 2 mm in depth except where the plateau-like islands of hyperplasia made it 5 mm. The pyramids were poorly defined against the light-red background.

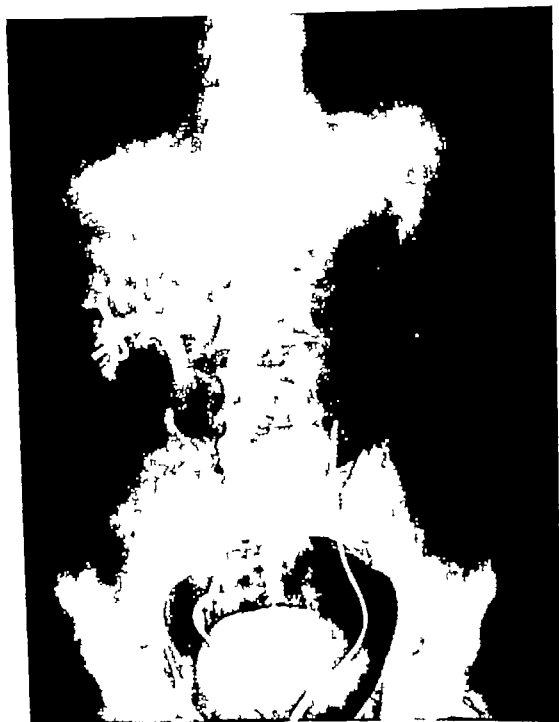


FIG. 21. CASE 12. PYELOGRAM OF RIGHT KIDNEY.

In the anterior half of the kidney was embedded a dark brown stone. The capsule of the left kidney stripped with ease, revealing a smooth, irregular surface. The cortex measured approximately 3 mm in depth. In the posterior half, at the base of one poorly defined pyramid, was a small, spherical stone. At the inferior pole there was a 'stag horn' stone, measur-

ing approximately 2.5 cm in diameter. The average circumference of the ureters was 1.5 cm. On the right, at the junction of the upper third with the lower portion, was a brown, cylindrical stone about 1 cm in length which



FIG 22 CASE 12 PYELOGRAM OF LEFT KIDNEY AND RENAL STONES OVER RIGHT

failed to occlude the lumen (Fig 23). The left ureter contained no stone. The anatomic diagnoses were bilateral chronic pyelonephritis and nephrolithiasis.

Histologic examination of the kidneys revealed healed pyelonephritis. The pelvis showed severe chronic inflammation. There was diffuse scar tissue throughout the kidney parenchyma. The glomeruli were slightly

reduced in number. Many showed periglomerular fibrosis, only a few showed alternative glomerulitis and sclerosis. There were no necrosed glomeruli. The tubules were occluded by casts and practically no functioning tubules were present. The arteries showed an unusually advanced degree of productive endarteritis. There was also a pronounced degree of hyperplastic arteriosclerosis, but no necrosis of the arterioles was seen. A few of the arterioles showed hyaline degeneration. The interstitial tissue

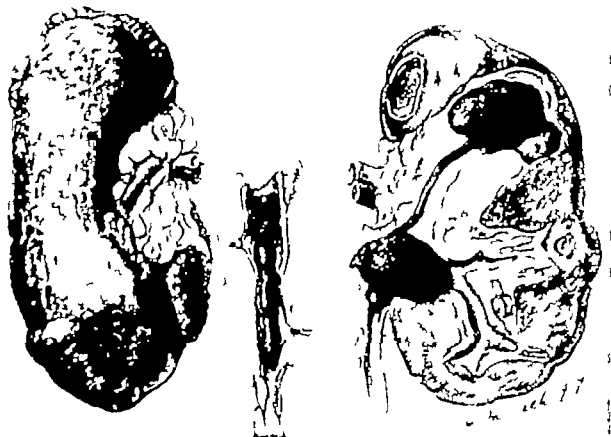


FIG. 23. CASE 12. GROSS APPEARANCE OF KIDNEYS. IRREGULAR SCARRING OF OUTER SURFACE OF RIGHT KIDNEY. RENAL STONES AND APPEARANCE OF CUT SURFACE OF LEFT KIDNEY. RIGHT URETERAL STONES (MIDDLE).

was increased and showed evidence of a severe degree of chronic inflammation.

Case 13. A 19-year-old single female entered the hospital in May, 1937, complaining of "difficulty in breathing." Ever since early childhood she had been below par. In childhood she suffered from scarlet fever, frequent sore throats, influenza and bronchopneumonia, and was told that she had kidney trouble. Three years previous to her admission she developed edema of the ankles and dyspnea on exertion. For 9 months she had had visual difficulty, for 3 months puffiness under the eyes and for 2 weeks attacks of smothering.

Soon after entering the hospital the patient developed a convulsion and lapsed into coma. There was a blowing systolic murmur. The arterial pressure was 245/215. There were bilateral Babinski and Oppenheim signs. The urine contained a heavy trace of albumin but the sediment was negative. The red blood cell count was 2,900,000 and the hemoglobin 56 per cent. The non-protein nitrogen was 200 mg. The spinal fluid pressure was 285. The patient died within 24 hours after onset of convulsions. The diagnoses were chronic nephritis and hypertension.



FIG 24 CASE 13 GROSS APPEARANCE OF KIDNEYS RENAL RICKETS TYPE RIGHT KIDNEY WEIGHED 20 GRAMS AND LEFT, 40 GRAMS

Postmortem examination revealed the following essential findings. The heart weighed 290 grams. The combined weight of the kidneys was 60 grams (Fig 24). The capsules stripped fairly easily. The left kidney was about twice the size of the right. The lower pole of the left kidney showed but a small amount of cortex and medulla remaining. The surface was coarsely and finely irregular. Crossing these elevations were many linear scars. The cut surface of the left kidney showed a pale, gray-pink cortex, poorly demarcated from the deeper pink medulla. Toward the lower pole the cortex was irregular, 0.2 to 0.5 cm in width, and only a very small amount of medulla was present. The right kidney was similar to the left, but was about one-half the size. The lower pole was almost

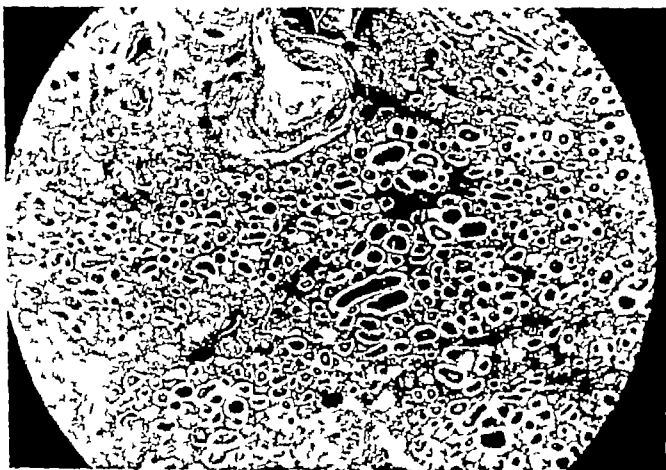


FIG. 25 CASE 13 SCARRED AREA WITH TUBULES FILLED WITH COLLOID CASTS
HYPERPLASTIC ARTERIOLOSCLEROSIS $\times 60$

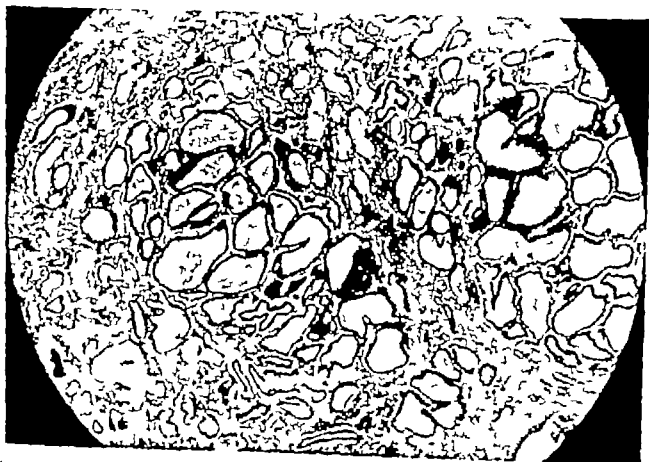


FIG. 26 CASE 13 TUBULES OUTSIDE OF SCARRED AREA SHOWING MARKED DILATATION
 $\times 60$

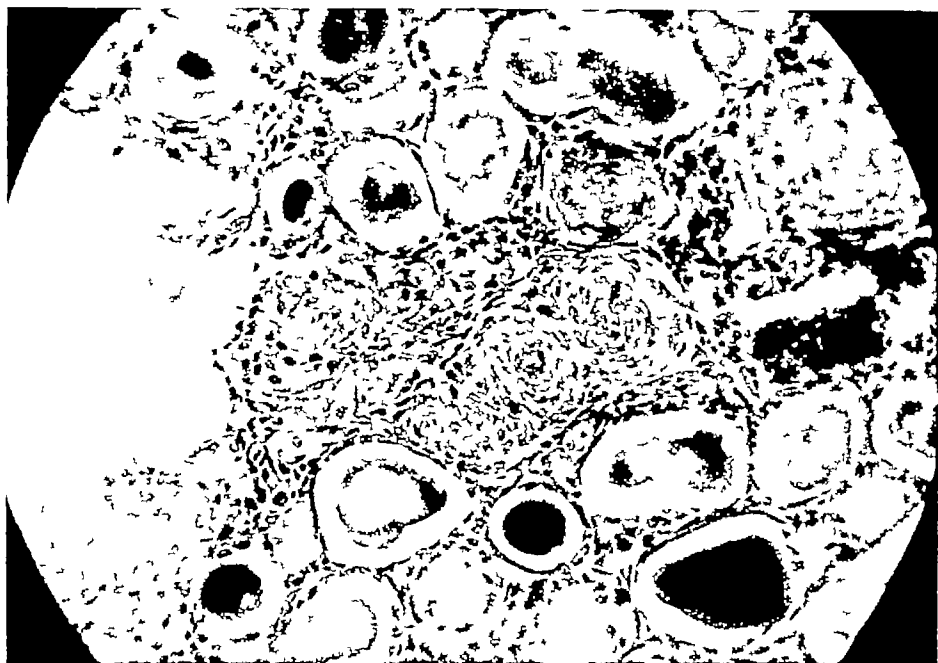


FIG 27 CASE 13 SCARRED AREA HYPERPLASTIC ARTERIOLOSCLEROSIS TUBULES
CONTAIN COLLOID CASTS $\times 300$

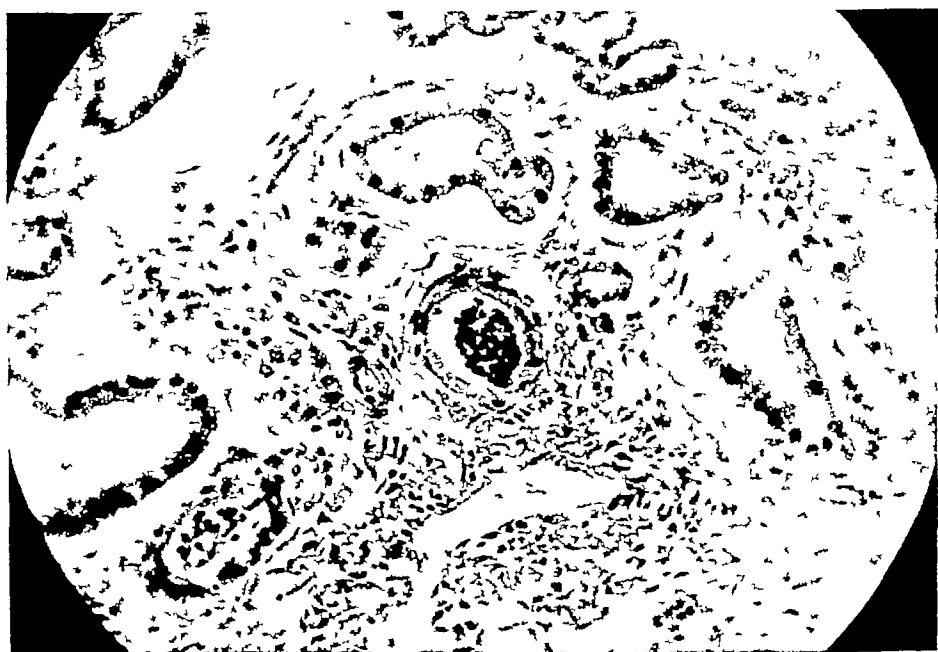


FIG 28 CASE 13 ARTERIOLES AND TUBULES IN NONSCARRED AREA ESSENTIALLY
NEGATIVE $\times 300$

entirely absent The cortex and medulla were very thin The pelves and ureters and the bladder were normal

Microscopic examination of the right kidney showed healed pyelonephritis The pelvis was infiltrated with lymphocytes No functioning glomeruli were present, all were sclerosed The tubules showed marked dilatation and they were occluded by casts The interstitial tissue was infiltrated with lymphocytes There was a severe degree of diffuse productive endarteritis and hyperplastic arteriolosclerosis Some of the arterioles showed necrosis The changes in the left kidney were essentially the same, but some functioning glomeruli were present and the number of occluded glomeruli was relatively small Some of the tubules contained pus The vascular changes were less pronounced and necrosis of the arterioles was not present. The adrenals were normal (Figs 25, 26, 27 and 28)

Case 14 A 26-year-old married female entered the hospital in January, 1935, complaining of vomiting and of attacks of convulsions She had suffered from frequent sore throats until the age of 13, when tonsillectomy was performed She had always had dyspnea on exertion At the age of 19 she developed rheumatic fever and was bedridden for 7 months She was told at that time that she had high blood pressure One month before her entrance into the hospital she had an hemoptysis Two days prior to admission she became suddenly unconscious while talking There was no definite history of pyuria, but there had been nocturia in the past

On examination there were a few patches of white exudate over the eyegrounds The heart was moderately enlarged, a presystolic thrill and murmur were present over the apex and a diastolic murmur over the aortic area The systolic arterial pressure was 200 to 240 and the diastolic 110 to 125 The urine contained albumin, but otherwise it was negative The red blood cell count was 4,000,000 and the hemoglobin 70 per cent The non protein nitrogen was 34 mg per 100 cc The phenolsulphonphthalein test was 30 per cent in 2 hours. The concentration dilution test showed a variation in specific gravity from 1.004 to 1.010 The patient improved while in the hospital The diagnoses were rheumatic heart disease and malignant nephrosclerosis with vascular crisis.

The patient was followed in the Outpatient Department between February and September, 1935 She suffered from headaches, from increasing dyspnea on exertion and from more pronounced nocturia The arterial pressure fluctuated between 220 and 240 systolic and between 120 and 150 diastolic. In September, 1935 she developed attacks of paroxysmal dyspnea and again entered the hospital Physical examination revealed essentially the same findings as before The arterial pressure varied between

200 and 255 systolic and between 120 and 140 diastolic. The urine contained albumin and, on three occasions, clumps of white blood cells. The red blood cell count varied between 3,600,000 and 2,100,000. The phenol-sulphonphthalein test was 3 per cent in 2 hours. The non-protein nitrogen rose from 67 to 235 in the course of 4 weeks. The patient gradually lapsed into coma. The diagnoses were rheumatic heart disease, pyelonephritis with arterial hypertension and with cardiac asthma.

Postmortem examination revealed the following essential findings. The heart weighed 400 grams. The mitral valve was thickened along the margin. The chordae tendineae were thickened and slightly shortened. The aortic valves were thickened. The lungs were congested. The combined weight of the kidneys was 100 grams. The capsule stripped with some difficulty. The surface was irregularly granular with depressed scars. The cut surface revealed a thin, irregular, pale-red cortex and scarred, red, indistinct pyramids. The pelves, ureters and bladder were normal. The anatomic diagnoses were healed rheumatic heart disease and bilateral pyelonephritis.

Microscopic examination of the kidneys revealed healed pyelonephritis with vascular changes. There was some alternative glomerulitis and marked sclerosis of the glomeruli. There was pronounced dilatation of the tubules with numerous casts. The interstitial tissue was increased and showed chronic inflammation. The vascular changes consisted in productive endarteritis and a pronounced degree of hyperplastic arteriosclerosis.

Case 15 This 24-year-old married female entered the hospital in May, 1935, complaining of difficulty in breathing ("smothering sensations") and recurrent failure of eyesight. Ever since early childhood she had been below par and had frequently suffered from severe headaches. Her best weight was 90 pounds. Her first pregnancy, 4 years previous to admission, ended prematurely. Her second pregnancy, 1 year later, ended at the sixth month, and the patient was told that she had high blood pressure and albuminuria. Following delivery the albumin disappeared and her blood pressure became lower. For 3 years thereafter the patient felt well except for headaches. Early in 1935 she was sent to a hospital for 2 weeks because of blurred vision. She was told that she had albuminuria and a blood pressure of "250". Two weeks previous to her admission she became nervous and developed numbness over the arms and legs.

On physical examination the patient showed marked pallor with slight puffiness under the eyes. There was bilateral papilledema with numerous white scars. The heart was not enlarged. The aortic second sound was

greater than the pulmonic second sound The blood pressure varied from 190/140 to 250/150 The veins of the neck and of the chest were distended The specific gravity of the urine varied from 1 006 to 1 012 The sediment contained from 10 to 20 or more white blood cells per high power field, with, at times, 2 to 3 red blood cells There were occasional granular casts The red blood cell count was 1,400,000 and the hemoglobin 35 per cent The Kahn test of the blood was negative The non protein nitrogen was 150 to 187 mg per 100 cc of blood The spinal fluid pressure was 350 mm H₂O The temperature was 100 to 101°F The electrocardiogram was normal

During her stay in the hospital the patient's urinary output decreased She developed increasing headaches and became psychotic A pericardial friction rub appeared and finally she fell into stupor and died of uremia

Postmortem examination revealed the following essential findings The heart weighed 340 grams The pericardium was covered with fibrinous shreds The combined weight of the kidneys was 90 grams The capsule stripped with difficulty, revealing a reddish surface with irregular scars and elevated nodules 1 to 3 mm in diameter The cortex was 2 to 3 mm in thickness The pelves, ureters and bladder were normal The diagnosis was chronic pyelonephritis

Microscopic examination of the kidneys revealed healed pyelonephritis Only a few glomeruli were present and the majority of these showed alterative glomerulitis The tubules were dilated and the majority were filled with casts, but contained no pus The renal pelvis showed chronic inflammation The interstitial tissue was markedly increased and showed chronic inflammation The larger arteries showed pronounced productive endarteritis There was pronounced hyperplastic arteriosclerosis as well as arteriolar necrosis.

Case 16 A 31 year old male entered the hospital in November, 1934, complaining of shortness of breath of 6 weeks' duration No history of urinary infection was obtained The essential findings were slight enlargement of the heart and accentuation of the aortic second sound The arterial pressure varied between 190 and 240 systolic and between 130 and 150 diastolic Numerous urine specimens showed variations in the specific gravity from 1 018 to 1 023 and a trace of albumin, the sediment was essentially normal The red blood cell count was 5,400,000, the hemoglobin 88 per cent and the white blood cell count 14,500 The non protein nitrogen was 30 to 33 mg per 100 cc The phenolsulphonphthalein test was 15 per cent in 2 hours The electrocardiogram showed partial heart block

with left ventricular preponderance. The Kahn test of the blood was negative. During his 4 weeks' stay in the hospital the patient had no complaints. The diagnosis was essential hypertension.

The patient worked until the end of May, 1935, when he became short of breath and on several occasions brought up blood-tinged sputum. In October, 1935 he reentered the hospital. There was a slight degree of papilledema with exudate over the eyegrounds. The heart was slightly enlarged. The blood pressure was 220/160 mm Hg. The urine was essentially as before. The non-protein nitrogen was between 49 and 66 mg. X-ray examination of the chest revealed fluid and congestion on both sides. The patient became drowsy, cyanotic and restless, and died.

Postmortem examination revealed the following essential findings. The left kidney weighed 60 grams. The capsule stripped with ease, leaving a grayish-red surface with scattered shallow depressions, from which projected, at varying distances, moderately firm, yellowish-gray nodules 1 to 2 mm in diameter. Cut section revealed a grayish-red cortex in which were scattered grayish-white fibrous streaks. The average thickness of the cortex was 2 mm. The pyramids were also markedly decreased in size and their striations were made out with difficulty. The pelvis was enlarged, but the calyces and ureter were normal. The right kidney was increased in size and weighed 320 grams. The capsule stripped with ease, revealing a smooth surface. The cortex was thickened and the interpyramidal cortex seemed to compress the medulla. Both ureters and the bladder were normal.

Microscopic examination of the left kidney showed a marked degree of healed pyelonephritis. There was chronic inflammation of the renal pelvis. All but a few of the tubules were plugged with casts, but they contained no pus. The glomeruli showed some sclerosis. The interstitial tissue was moderately increased and was infiltrated with lymphocytes. The arteries showed productive endarteritis. There was a marked degree of hyperplastic arteriosclerosis and some necrotizing arteriolitis. The right kidney showed no pyelonephritis and only slight vascular changes. In this case again the vascular changes were more marked in the areas of infection.

Case 17 This 28-year-old married female entered the hospital in March, 1933 in labor. In 1927 she had suffered from acute purulent otitis media. In 1928, 1930 and 1933 she had had pregnancies which ended in premature stillbirths (Chart 4). There was albuminuria with each of these pregnancies and the blood pressure was elevated. In 1930 in the prenatal clinic the blood pressure was 210/140. The urine sediment was negative.

on repeated examinations In 1933 before delivery the systolic blood pressure was 180 to 220 and the diastolic 120 to 140 In the course of 4 days after delivery the blood pressure came down, but later rose to 160/110 On subsequent examinations the arterial pressure was lower The urine was essentially negative.

The patient was readmitted to the hospital in February, 1936 because of sudden coma of 3 days' duration She became rational again but subsequently lapsed into unconsciousness The veins of the eyegrounds were

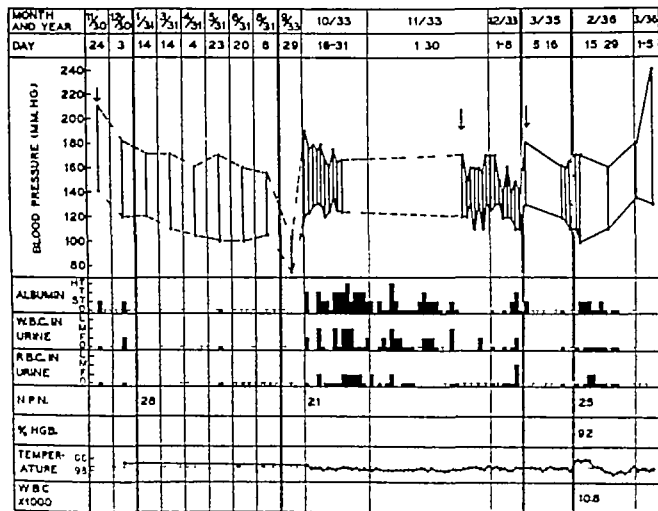


CHART 4 FEATURES OF CLINICAL COURSE IN CASE 17

tortuous The discs were blurred and there were hemorrhages of all sizes. There were bilateral Kernig, Babinski and Oppenheim signs The specific gravity of the urine ranged from 1.006 to 1.012 and there was an occasional trace of albumin The non protein nitrogen was 25 mg The Kahn test was negative. The spinal tap yielded bloody fluid The temperature was 98.4 to 100°F The patient became conscious and complained of severe headache Subsequently she again fell into coma and died Diagnoses were subarachnoid hemorrhage, malignant hypertension and nephrosclerosis

The essential findings on postmortem examination were as follows. The heart was enlarged, weighing 400 grams, and there was moderate hypertrophy of both ventricular walls. The mitral orifice was somewhat narrowed. There was thickening and interadherence of the cusps. The chordae tendineae were shortened and thickened. The aortic cusps showed changes similar to those in the mitral valve. The lungs contained considerable frothy, blood-stained serous fluid. The kidneys weighed 200 grams. The capsules stripped with ease. The surface was irregular, with flat-

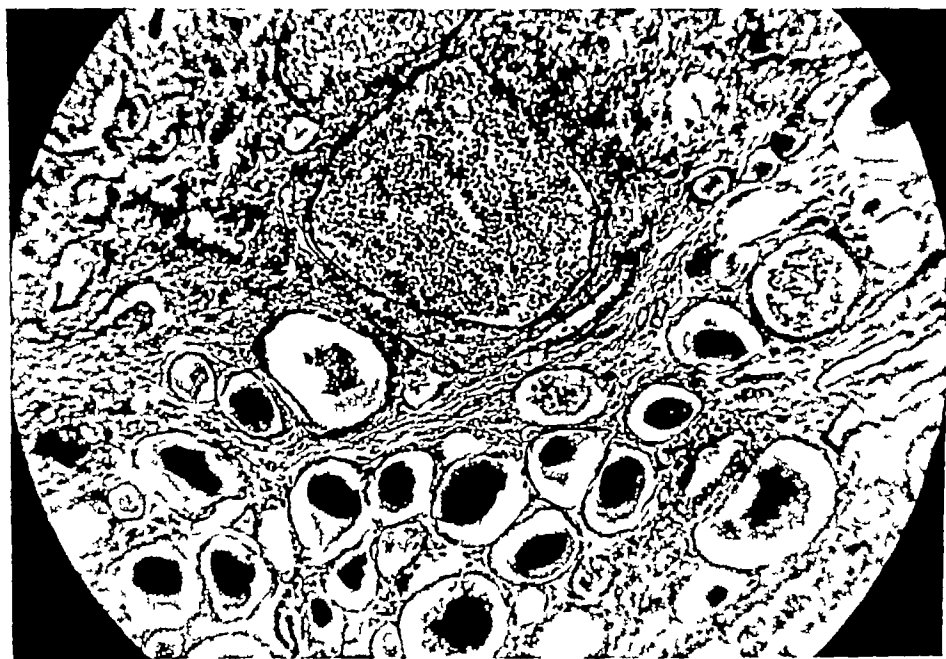


FIG 29 HEALED, RECURRENT ACUTE PYELONEPHRITIS. SOME TUBULES CONTAIN COLLOID CASTS, OTHERS ARE FILLED WITH LEUKOCYTES. $\times 140$

based depressions, and sections revealed a purple cortex 7 mm thick which was poorly demarcated from the purple pyramids. The pelves, ureters and bladder were normal. The anatomic diagnoses were healed rheumatic aortic and mitral valvulitis, pulmonary congestion and edema, pyelonephritis.

Microscopic examination revealed healed pyelonephritis with a severe degree of productive endarteritis and hyperplastic arteriosclerosis in the scars.

Healed and recurrent pyelonephritis

Patients who have had attacks of pyelonephritis tend to have recurrence, which frequently develops on a previously healed pyelonephritic kidney. Thus both the clinical and the histologic changes represent the combined picture of healed pyelonephritis and, in addition, of acute or chronic active pyelonephritis (Fig. 29). Clinical separation of this group from the group with chronic pyelonephritis is often not feasible. The diagnosis can be made only on the basis of histologic examination. We have studied 30 cases with healed recurrent pyelonephritis. The ages of these patients varied from 9 to 56, 21 were males and 9 females. Cases 7 and 8 were examples of healed and recurrent pyelonephritis. In view of the foregoing discussion, this type of pyelonephritis requires no further description.

VASCULAR CHANGES IN PYELONEPHRITIS AND THEIR RELATION TO
ARTERIAL HYPERTENSION

Since our original interest in this investigation was in the relation of pyelonephritis to hypertension, we have studied the vascular changes in considerable detail. The following are the observations which we have made.

In acute pyelonephritis the inflammatory process occasionally involved both arterioles and venules. The nature of the involvement varied. In some patients the lesion consisted of a deposition of fibrin in the wall of an arteriole and of infiltration of polymorphonuclear leukocytes and mononuclear cells. In others there was more extensive, acute involvement, leading to partial or complete thrombosis of the vessel lumen with infiltration of polymorphonuclear leukocytes into the wall. On the whole, such acute vascular lesions were not common.

In chronic or healed pyelonephritic kidneys, vascular lesions of varying severity were often prominent and deserve special description. In general, the vascular lesions were most marked in the inflamed, scarred areas (Figs. 30 and 31). In addition, in cases of unilateral pyelonephritis the vascular changes were always most marked on the involved side. This was true irrespective of whether or not the patient had had hypertension.

The vascular changes may be divided into those affecting the arteries and those involving the arterioles. The lesions in the arteries consisted in increased connective tissue in the intima. This increased connective tissue was often of the basophilic reticular type seen in "primary" malignant hypertension. In other cases it was denser and tended to be acidophilic. Associated with this type of change, there was reduplication of the internal elastic membrane. In addition,

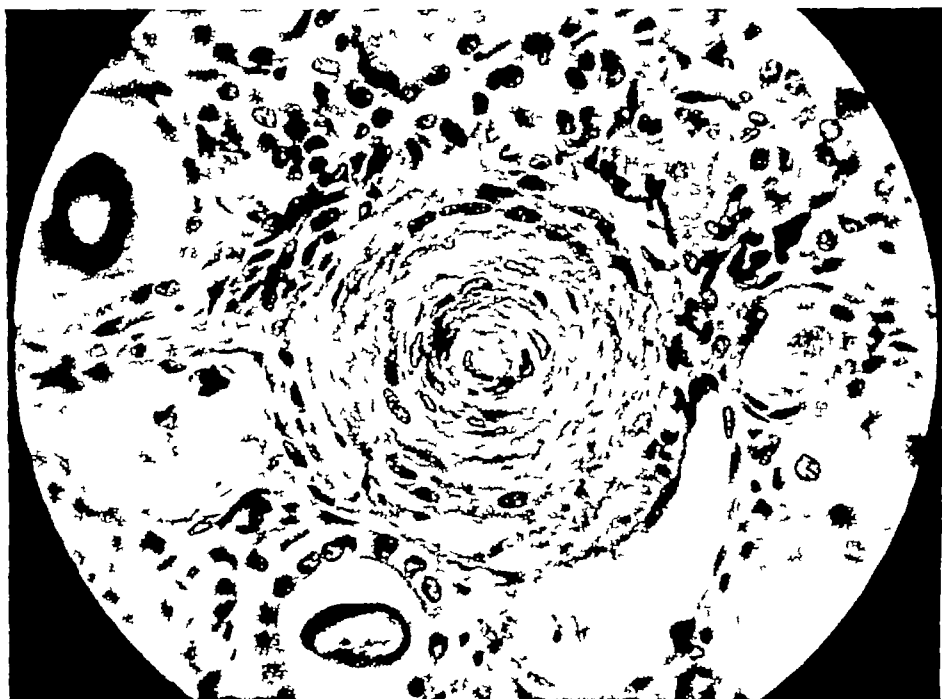


FIG 30 HEALED, RECURRENT ACUTE PYELONEPHRITIS. HYPERPLASTIC ARTERIOLOSCLEROSIS IN SCARRED AREA. $\times 550$

there was a medial hypertrophy in some cases. We have included the arterial lesions under the term "productive endarteritis."

The changes in the arterioles were usually those characteristic of hyperplastic arteriosclerosis, i.e., thickening of the walls due to concentric proliferation of the cells, often associated with an increase in collagen. Hyalinization of the arteriolar walls, as seen in benign nephrosclerosis, was relatively uncommon. Such hyaline degeneration of the arterioles occurred relatively more often in the older group,

and was usually considered to be a result of a morbid process independent of pyelonephritis. In a certain number of cases arteriolar necrosis was present as well as arteriosclerosis. This was evidenced by smudging or blurring of the vessel wall, with hemorrhage into the wall, karyorrhexis of the nuclei and infiltration of a certain number of cells, both polymorphonuclear leukocytes and mononuclear cells. In some instances examples of healed necrotizing arteriolitis were

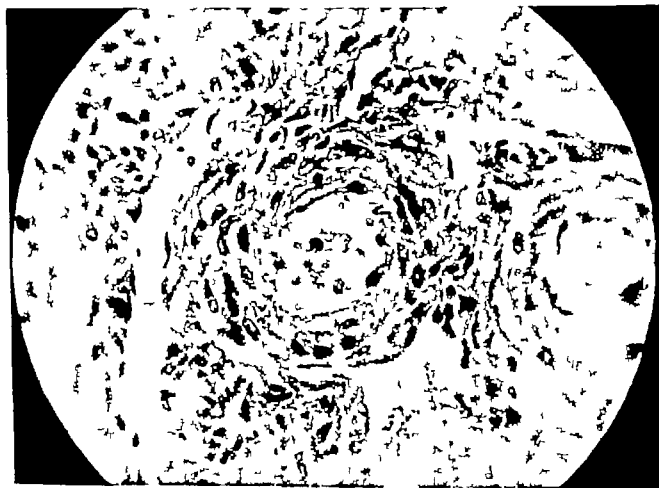


FIG. 31 ARTERIOLE FROM SAME KIDNEY AS IN FIGURE 30 BUT FROM NONSCARRED AREA. SLIGHT HYPERPLASTIC ARTERIOLOSCLEROSIS. $\times 550$

present. Such lesions showed vessels with thickened walls infiltrated with pigment laden macrophages, and in some instances vessels with lumens partially or completely obliterated as a result of the ingrowth of fibroblasts.

It might well be argued that the vascular changes described above are merely secondary to the decreased function of the scarred portions of the kidney. In order to exclude or confirm this thesis, blood vessels in a variety of conditions were studied.

The first of this control group were cases with tuberculous kidneys. It is generally recognized that hypertension is rarely associated with uncomplicated renal tuberculosis. Hence this group seemed to be of especial importance for us. The arteries in such cases of renal tuberculosis either showed no change or a slight degree of intimal thickening. Likewise, the arterioles were essentially negative, except for an occasional slight degree of hyalinization. Vascular changes analogous to those described in pyelonephritis were present in a few cases, but these cases presented a combination of tuberculosis and pyogenic pyelonephritis.

The second control group comprised ovaries and uteri of women past the menopause, for here we felt could be studied involutionary vascular changes due to decreased function. The arteries of the ovaries showed a high degree of collagenous intimal thickening, often with hyalinization, with increase in the elastic tissue not only in the intima but also in the adventitia. The media of these vessels was often greatly thinned, in some instances consisting of only a few muscle fibers. The arterioles showed slight to moderate hyperplastic arteriosclerosis and, not infrequently, hyalinization. There was marked increase of elastic tissue in the intima and adventitia with, in addition, some sclerosis of the adventitial tissue. The changes in the uterine arteries were similar to those in the ovary but were more extensive, often resulting in obliteration of the lumens (Fig. 32). The arterioles were hyalinized and there was an increased amount of elastic tissue in the adventitia. Hyperplastic arteriosclerosis was rare and, when present, was only slight.

Sohma (26) has attributed certain of the vascular changes in these organs to the effect of the menstrual cycle. Therefore we examined, in addition, the ovaries and uteri of young women. In this group was found slight to moderate hyperplastic arteriosclerosis in the ovaries, but the arterial changes were slight in contrast to those observed in the postmenopausal cases. The arteries in the uteri were essentially negative, an occasional arteriole showed a slight degree of hyperplastic sclerosis.

As a result of the study of this group we felt that involutionary changes or changes due to decreased function present a fairly char-

acteristic picture (Fig 32) The intima of the arteries is greatly thickened owing to increased connective tissue which often undergoes hyalinization The media tends to be thinned, often to a high degree There is a marked increase of elastic tissue, not only in the intima but also in the adventitia The arteriolar changes consist in hyalinization with increase in elastic tissue in the intima and adventitia The hyperplastic type of arteriosclerosis noted especially in the ovaries is to be regarded, as suggested by Sohma, as the result of functional



FIG 32 ARTERY FROM SENILE UTERUS SHOWING MARKED THICKENING OF INTIMA AND THINNING OF MEDIA

activity, since it is seen in young persons as well as in old Arterial changes similar in character to those described in the ovaries and uteri have long been recognized, in addition, in connection with chronic or old tuberculous processes with cavitation in the lungs

As a result of the foregoing studies we came to the conclusion that involutionary vascular changes usually present a picture quite different from the changes described in pyelonephritic kidneys On reviewing our material we found that in some cases of pyelonephritis there were

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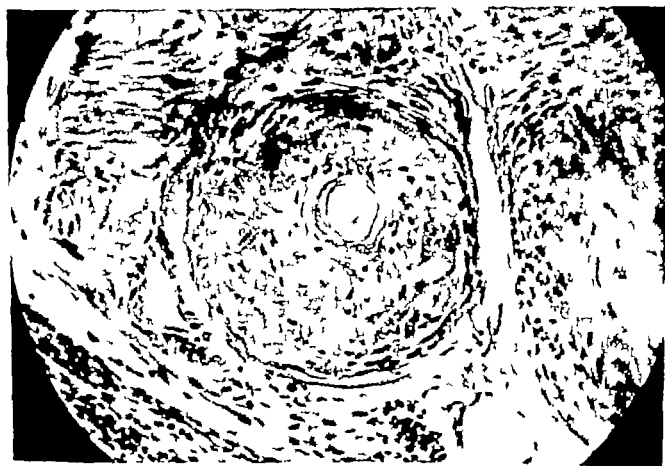


FIG 32 ARTERY FROM SENILE UTERUS SHOWING MARKED THICKENING OF INTIMA AND THINNING OF MEDIA

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involutionary as well as proliferative changes and that these could be readily distinguished (Fig 33)

Since the vascular changes in tuberculous kidneys with marked destruction of the parenchyma do not consist in productive endarteritis or hyperplastic arteriolosclerosis, as seen in pyelonephritic kidneys, and because it is possible to distinguish physiologic or involutionary vascular sclerosis as well as the sclerosis occurring in benign nephrosclerosis, we feel that the vascular changes in pyelonephritis described

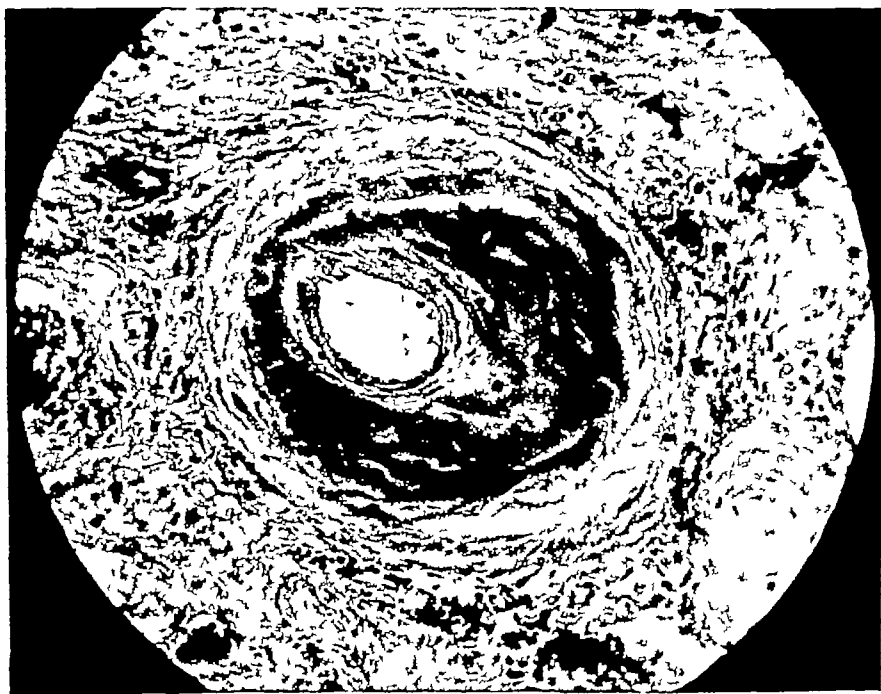


FIG 33 HEALED PYELONEPHRITIS ARTERY IN SCAR WITH TYPE OF CHANGE SIMILAR TO THAT SHOWN IN FIGURE 32

above can be attributed directly to the inflammatory conditions in the kidney. In further support of this contention is the fact that in a group of cases with hydronephrotic kidneys with scarring and atrophy but without complications of pyelonephritis no similar vascular changes were found, thus again emphasizing the effect of inflammation on the blood vessels.

An analysis of the relation between hypertension and the arterial lesions observed has brought out the following facts (Tables I and

II) (1) When hypertension was present the vascular changes were always more marked and diffuse, they were more marked in scarred areas and, in cases of unilateral pyelonephritis, on the pyelonephritic side (2) In cases without hypertension no significant vascular lesions were found except in the scars, and here they were slight to moderate In unilateral pyelonephritis, vascular changes occurred only on the affected side (3) In unilateral pyelonephritis, if vascular lesions were observed on both sides then hypertension was always present

TABLE I
Cases of pyelonephritis with normal blood pressure

SEX	AGE	ARTERIAL BLOOD PRESSURE	HEART WEIGHT	KIDNEY WEIGHT	RENAL VASCULAR CHANGES			PYELONEPHRITIS	CAUSE OF DEATH
					P E.	H A.	N A.		
	years	mm Hg	grams	grams					
F	10	100/40	180	360	0	0	0	Chronic	Pneumonia
F	23	130/70	220	60	++	++	0	Chronic	Uremia
M	25	130/60	450	200	+	+	0	Chronic	Uremia
F	26	130/80	240	220	+	+	0	Chronic	Cerebral
F	27	130/90	350	375	0	0	0	Acute	Collapse
F	39	100/64		410	+++	0	0	Chronic	Pneumonia
F	42	120/80	475	235	+++	0	0	Healed	Cerebral
F	50	90/30	275	225	0	+	0	Healed	Pneumonia
M	52	130/90	330	400	++	0	0	Chronic	Uremia
M	52	110/50	280	250	++	+	0	Healed	Pneumonia
M	61	110/80	750	400	++	0	0	Healed	Cardiac
M	69	120/80		525	+	0	0	Chronic	Uremia
M	72	80/50	280	330	0	0	0	Acute	Sepsis

P E., productive endarteritis. H A., hyperplastic arteriosclerosis. N A., necrotizing arteriolitis.

In order further to evaluate this interrelation between vascular changes and arterial hypertension we have compared the degree and the type of vascular changes in four groups of cases with *bilateral pyelonephritis* (A) Cases with normal blood pressure but without uremia, (B) cases with normal blood pressure and uremia, (C) cases with high blood pressure but without uremia, (D) cases with high blood pressure and uremia. The results of this comparison indicate that in groups A and B there was usually a slight degree of hyperplastic arteriosclerosis. In groups C and D, on the other hand, the vascular

changes consisted in pronounced hyperplastic arteriolosclerosis. In group *D*, in addition, there was frequently necrosis of the arterioles. It is of particular interest that the vascular changes in group *A* were identical in character with those occurring in groups *C* and *D* but less

TABLE II
Cases of pyelonephritis with severe hypertension

SEX	AGE	ARTERIAL BLOOD PRESSURE	HEART WEIGHT	KIDNEY WEIGHT	RENAL VASCULAR CHANGES			PYELONEPHRITIS	CAUSE OF DEATH
					P E	H A	N A		
	years	mm Hg	grams	grams					
F	12	220/160	230	120	++	+++	+	Unilaterally chronic	Intestinal infarction
F	18	220/130	320	61	+	++	0	Chronic—recurrent	Uremia
F	19	250/220	290	62	+++	+++	+	Recurrent	Uremia
F	23	260/190		113	+++	+++	++	Recurrent	Uremia
F	24	250/160	340	90	++	+++	++	Healed	Uremia
F	27	260/150	400	100	++	+++	0	Healed	Cerebral
F	28	240/140	400	200	++	+	0	Healed	Cerebral
M	32	280/130	430	90	++	+++	+	Recurrent	Uremia
F	34	240/140	480	120	+++	+++	0	Healed	Uremia
M	40	240/160	560	170	++	+++	0	Healed	Uremia
F	40	270/160	480	210	+++	+++	++	Chronic	Uremia
M	41	250/150	480	200	++	+++	0	Healed	Subarachnoid hemorrhage
M	41	220/140	720	320	++	+	0	Chronic	Cardiac
M	42	210/120	590	115	++	+++	0	Recurrent	Cerebral
F	46	260/170	465	240*	++	+++	+++	Recurrent	Uremia
F	54	240/140	570	225	+++	+++	0	Healed	Cardio cerebral
F	55	230/180	580	195	+++	+++	0	Recurrent	Uremia
M	59	260/150	640	280	+++	+++	++	Healed	Uremia
M	62	245/100	600	220*	+++	++	0	Recurrent	Cardiac

P E, productive endarteritis H A, hyperplastic arteriolosclerosis N A, necrotizing arteriolitis

* Right only

severe and extensive. This suggests that the initial vascular changes, which ultimately are associated with "malignant" hypertension, i.e., hyperplastic arteriolosclerosis, occur *before* the development of arterial hypertension.

That pyelonephritis is responsible for the vascular changes is

indicated by the presence of vascular changes in cases with *unilateral pyelonephritis* (Fig 34) In these cases more advanced vascular lesions can occur in the affected kidney in the presence of normal blood pressure than in cases with bilateral pyelonephritis and normal arterial pressure Table III presents the data on 20 cases of unilateral chronic or healed pyelonephritis The size of the affected kidney was usually greatly diminished, while the unaffected kidney was often enlarged

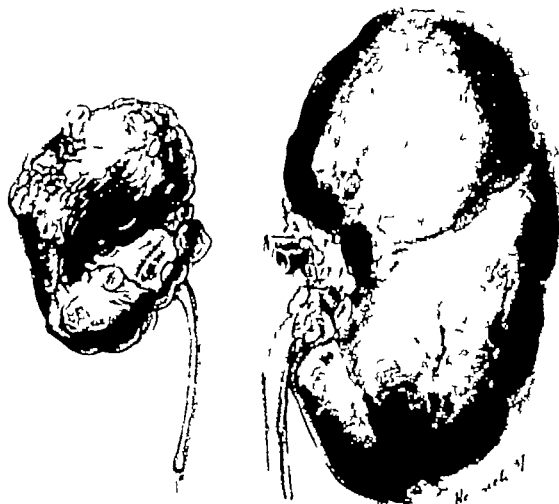


FIG 34 EXAMPLE OF UNILATERAL PYELONEPHRITIS IN 50-YEAR OLD PATIENT

Of the 20 cases, with ages varying from 7 months to 81 years 8 showed normal blood pressure 14 died of uremia and 3 of associated severe hypertension The vascular changes in the affected kidney in cases with normal blood pressure varied from moderate to severe the unaffected kidney showed no changes of significance In cases with hypertension the affected kidney showed marked vascular changes while the unaffected kidney showed slight to moderate

changes consisted in pronounced hyperplastic arteriolosclerosis. In group *D*, in addition, there was frequently necrosis of the arterioles. It is of particular interest that the vascular changes in group *A* were identical in character with those occurring in groups *C* and *D* but less

TABLE II
Cases of pyelonephritis with severe hypertension

SEX	AGE	ARTERIAL BLOOD PRESSURE	HEART WEIGHT	KIDNEY WEIGHT	RENAL VASCULAR CHANGES			PYELONEPHRITIS	CAUSE OF DEATH
					P E	H A	N A		
	<i>years</i>	<i>mm Hg</i>	<i>grams</i>	<i>grams</i>					
F	12	220/160	230	120	++	+++	+	Unilaterally chronic	Intestinal infarction
F	18	220/130	320	61	+	++	0	Chronic—recurrent	Uremia
F	19	250/220	290	62	+++	+++	+	Recurrent	Uremia
F	23	260/190		113	+++	+++	++	Recurrent	Uremia
F	24	250/160	340	90	++	+++	++	Healed	Uremia
F	27	260/150	400	100	++	+++	0	Healed	Cerebral
F	28	240/140	400	200	++	+	0	Healed	Cerebral
M	32	280/130	430	90	++	+++	+	Recurrent	Uremia
F	34	240/140	480	120	+++	+++	0	Healed	Uremia
M	40	240/160	560	170	++	+++	0	Healed	Uremia
F	40	270/160	480	210	+++	+++	++	Chronic	Uremia
M	41	250/150	480	200	++	+++	0	Healed	Subarachnoid hemorrhage
M	41	220/140	720	320	++	+	0	Chronic	Cardiac
M	42	210/120	590	115	++	+++	0	Recurrent	Cerebral
F	46	260/170	465	240*	++	+++	+++	Recurrent	Uremia
F	54	240/140	570	225	+++	+++	0	Healed	Cardio cerebral
F	55	230/180	580	195	+++	+++	0	Recurrent	Uremia
M	59	260/150	640	280	+++	+++	++	Healed	Uremia
M	62	245/100	600	220*	+++	++	0	Recurrent	Cardiac

P E, productive endarteritis H A, hyperplastic arteriolosclerosis N A, necrotizing arteriolitis

* Right only

severe and extensive. This suggests that the initial vascular changes, which ultimately are associated with "malignant" hypertension, i.e., hyperplastic arteriolosclerosis, occur *before* the development of arterial hypertension.

That pyelonephritis is responsible for the vascular changes is

indicated by the presence of vascular changes in cases with *unilateral pyelonephritis* (Fig 34) In these cases more advanced vascular lesions can occur in the affected kidney in the presence of normal blood pressure than in cases with bilateral pyelonephritis and normal arterial pressure Table III presents the data on 20 cases of unilateral chronic or healed pyelonephritis The size of the affected kidney was usually greatly diminished, while the unaffected kidney was often enlarged

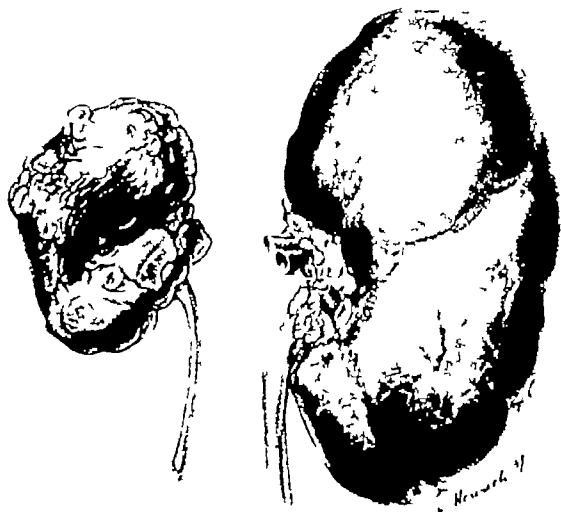


FIG 34 EXAMPLE OF UNILATERAL PYELONEPHRITIS IN 50-YEAR OLD PATIENT

Of the 20 cases, with ages varying from 7 months to 81 years, 8 showed normal blood pressure Four died of uremia and 3 of associated severe hypertension The vascular changes in the affected kidney in cases with normal blood pressure varied from moderate to severe the unaffected kidney showed no changes of significance In cases with hypertension the affected kidney showed marked vascular changes while the unaffected kidney showed slight to moderate

TABLE III
Cases of chronic unilateral pyelonephritis

SEX	AGE	HEART WEIGHT grams	KIDNEY A (PYELONEPHRITIC)					KIDNEY B (NONPYELONEPHRITIC)					BLOOD PRESSURE mm Hg	UREMIA
			Weight	Vascular changes			Pyelonephritis	Weight	Vascular changes			Pyelonephritis		
				P E	H A	N A			P E	H A	N A			
		grams					grams							
F	7/12	29	+	++	0	Chronic left	160	0	0	0	0 right	102/45	-	
F	10	180	++	±	0	Chronic right	95	0	0	0	0 left	250/180	-	
F	10	220	++	++	0	Chronic left	110	++	++	+	0 right	125/80	-	
F	12	230	++	++	++	Healed left	20	0	0	0	0 right	240/140	-	
F	26	240	+	+	0	Chronic left	320	+	+	0	0 right	130/80	-	
M	31	60	++	++	++	Healed left	180	++	+	0	0 left	240/150	+	
F	43	475	++	±	0	Healed right	240	+	+	0	Acute right	170/100	-	
F	46	465	++	++	++	Chronic left	260	0	0	0	0 left	210/100	-	
F	50	260	++	++	0	Healed right	140	+	0	0	0 right	110/70	+	
M	53	90	++	++	+	Chronic left	220	++	±	0	Acute right	240/140	+	
M	53	30	++	++	0	Healed left	160	++	++	0	0 left	170/100	+	
F	54	570	++	++	+	Healed right	160	++	±	0	0 right	185/80	-	
F	57	360	++	++	0	Healed left	140	++	0	0	Acute right	260/150	+	
F	58	300	++	0	0	Chronic left	200	++	++	++	0 left	180/120	-	
M	59	640	++	++	++	Healed right	360	0	0	0	0 left	150/110	-	
M	61	750	++	++	0	Healed right	230	++	0	0	0 left	135/65	-	
M	66	500	++	+	0	Healed right	170	0	0	0	0 right	170/90	-	
F	70	580	++	++	0	Healed left	300	0	0	0	0 left	150/80	-	
F	73	400	++	++	0	Healed right	315	++	0	0	0 left		-	
M	81	335	++	++	0	Healed right							-	

P E, productive endarteritis H A, hyperplastic arteriosclerosis. N A, necrotizing arteriolitis

changes Necrotizing arteriolitis was present on the affected side in 6 cases, but in only 2 of these cases did the unaffected kidney show this lesion. In several instances the weight of the affected kidney was similar to that in the group of so-called "renal rickets" (p 288). In contrast, however, the patients with small unilateral pyelonephritic kidneys could survive to middle or old age since the other kidney was competent. These findings indicate that marked bilateral hyperplastic arteriosclerosis is always associated with hypertension. The existence of a definite relationship between the degree of vascular change and hypertension is also attested by the fact that from a study of the renal vascular lesions alone, the probability of the presence of arterial hypertension during life can be postulated with a remarkable degree of accuracy.

The question arises as to whether the advancing arterial lesions caused by the tissue inflammation in pyelonephritis are responsible for the hypertension, or whether the hypertension, caused by unknown factors, is responsible for the vascular changes. Because the vascular changes are more marked in the pyelonephritic scars and in the unilateral pyelonephritic kidney and because moderately severe arteriolar lesions are present in cases with pyelonephritis without hypertension, we conclude that the primary cause of the vascular changes is the inflammation (chronic or healed) due to pyelonephritis. However, as indicated also by the presence at times of arteriolar lesions in the unaffected kidney in cases with unilateral pyelonephritis (5 out of 20 cases), hypertension, in turn, is considered to be responsible for acceleration or for intensification of the arterial changes (26a). *Thus in the development of vascular changes we are dealing with a vicious circle precipitated by pyelonephritis and, in turn, accentuated and accelerated by hypertension.*

It should be pointed out, however, that a large proportion of cases of unilateral pyelonephritis with severe hypertension show no vascular changes in the unaffected side. This finding further supports the thesis that pyelonephritis is responsible for vascular changes and these changes, in turn, for hypertension.

In rare instances, on the other hand, arterial hypertension of moderate degree may be present without the type of vascular changes described. Thus, in 2 cases of renal rickets a moderate degree of

hypertension was present without hyperplastic arteriolosclerosis. In these 2 cases the marked diminution in the size of the kidney is presumably related to the elevation of the arterial pressure. Chanutin and Ferris (27) have shown that in the rat surgical removal of a portion of the renal parenchyma below a critical level is followed by arterial hypertension. It is also clear that elevation of the arterial pressure in pyelonephritis cannot be attributed to renal failure, because it is often present with adequate kidney function and, contrariwise, patients with uremia may have normal blood pressure (9, 22).

Comparison of vascular changes in pyelonephritis with those in nephrosclerosis

The histologic differential diagnosis of benign and malignant nephrosclerosis depends on the type of vascular changes. The characteristics of such vascular changes are widely recognized and we are summarizing them here only for reasons which appear below.

In benign nephrosclerosis the arteries show intimal thickening. This thickening is due to increased, dense connective tissue which stains acidophilically and not infrequently undergoes some degree of hyalinization. In addition there is splitting and reduplication of the internal elastic membrane, often to a marked degree. The characteristic lesion of the arterioles is a hyaline degeneration of their walls. To be of significance such arterial and arteriolar changes should occur more or less diffusely, and not be confined to small vascular scars.

The arterial changes in malignant nephrosclerosis consist in a thickening of the intima due to increase in both fibroblastic cellular and intercellular elements. The fibroblasts appear as cells with distinct processes embedded in an intercellular matrix which tends to stain basophilically and resembles mucous connective tissue. The internal elastic membrane may show but little change or may be thickened or reduplicated and in addition delicate elastic fibrils may be found in the intima. Arterial lesions similar to those described under benign nephrosclerosis also occur but as a rule the intimal connective tissue tends to be less dense and more cellular. The most characteristic and pathognomonic lesion is found in the arterioles. This lesion is hyperplastic arteriolosclerosis. It consists in a marked

thickening of the vessel walls due to concentric proliferation of cells, giving an onion-layer-like appearance to the walls. Between the cells occur delicate bundles of collagen. Necrotizing arteriolitis in our opinion is dependent on renal failure and hence cannot be regarded as essential for the diagnosis of malignant hypertension.

Both types of arterial vascular changes may be found in the same kidney, especially in the older age group who have long-continued hypertension of a moderate degree but who eventually develop severe hypertension and, not infrequently, renal failure, this group represents, in our opinion, the "Umschlag" type (Volhard).

From the foregoing description it is evident that the vascular changes in pyelonephritis are similar to or identical with those occurring in "primary" malignant hypertension, namely, productive endarteritis and hyperplastic arteriolosclerosis. These two vascular changes, we believe, are characteristic and diagnostic, from a morphologic point of view, of malignant hypertension. While it is true that the most marked changes were observed in those patients with hypertension, moderate and even severe changes were found focally in the absence of hypertension. As stated above, we believe that such changes are dependent on the inflammatory changes in the kidney. By this we do not mean actual extension of the pyogenic infection to the vessel wall, but the combination of edema, stasis and the products of the *inflammation*, which is often, although not always, a response to infection. Thus the mechanism of the development of these vascular lesions in the kidney is not unlike that in the lung (28) and in other organs. The type of pathogenesis described does not exclude other possible mechanisms in the production of hyperplastic arteriolosclerosis.

It is well recognized that malignant hypertension is usually a generalized vascular disease, i.e., the vascular lesions are by no means confined to the kidneys but are found in other organs, such as the pancreas, adrenals and gastrointestinal tract. These vascular changes include hyperplastic arteriolosclerosis and arteriolar necrosis. The fact that pyelonephritis is a disease in which the primary morbid changes are localized in the kidneys constitutes evidence that associated hypertension might be of renal origin, in contrast to what might be termed essential or "primary" malignant hypertension, which

is often from the onset a generalized vascular disease. It seemed important, therefore, to compare the degree and the character of the vascular changes in other organs in the two groups. In the pyelonephritic group with severe hypertension the vascular changes in other organs were for the most part absent or of only mild degree in comparison with those in the other group. The changes were rarely of the proliferative type and, in addition, the arteriolar necrosis in other organs was comparatively rare. These findings seem to strengthen the belief that "primary" malignant hypertension is a generalized vascular disease, while hypertension following pyelonephritis is primarily a renal vascular disease. It is also of interest that in diseases associated with generalized arteritis, such as lupus erythematosus, periarteritis nodosa and rheumatic fever, hypertension is present only when the arterioles of the kidney are rather extensively affected. Even when the arteritis is generalized but affects only the larger vessels, marked arterial hypertension does not develop. This suggests that in these diseases, too, hypertension depends on renal vascular changes.

CHRONIC PYELONEPHRITIS WITH SMALL KIDNEYS ("RENAL RICKETS") AND ITS RELATION TO RENAL HYPOPLASIA AND AGENESIS

One group of cases of pyelonephritis in our series deserves special mention. These cases were characterized by marked reduction in the size of the kidneys, the combined weights varying from 140 to 60 grams. The majority of these cases occurred in young patients below the age of 30. All of them died of uremia. In addition, except for 1 case (and this case had but one blood pressure reading) they all showed moderate or severe arterial hypertension. Among the patients with a history of pregnancy, toxemia occurred with high frequency (6 out of 8) (Table IV).

Grossly the kidneys presented one of two pictures: either a pale, coarsely granular or nodular surface, with or without depressed scars, or a surface characterized by flat areas alternating with nodular, adenoma-like projections (Fig. 24). The latter type resembled the picture presented by healed, acute yellow atrophy of the liver with the flat, scarred areas and adenoma-like areas of regeneration. A few cases showed dilatation of the ureters. An occasional pelvis was

dilated. The bladders were negative. No obstruction or anomalies were found in any case. The capsules stripped with difficulty, the cortices were narrowed and the markings indistinct. Histologically the flat, scarred areas showed the picture of healed or chronic pyelonephritis, as described above, with perhaps more complete obliteration of the glomeruli than was seen in the larger kidneys. The nodular and adenoma-like areas showed marked dilatation of the tubules.

TABLE IV
Cases of pyelonephritis with small kidneys ("renal rickets")

SEX	AGE	HEART WEIGHT	KIDNEY WEIGHT	VASCULAR CHANGES			ARTERIAL BLOOD PRESSURE	UREMIA	PYELONEPHRITIS
				P. E.	H. A.	N. A.			
	YEARS	GRAMS	GRAMS				mm. Hg		
F	18	320	61	+	++	0	220/130	+	Chronic
F	19	290	62	+++	++	+	245/215	+	Chronic
M	19	250	100	0	±	0		?	Healed
F	20	380	110	+++	+++	±	220/130	+	Healed
F	22	240		±	++	0	144/74	+	Healed
F	23	220	60	++	+	0	125/65	+	Healed
F	23		113	+++	+++	+	260/180	+	Chronic
F	24	320	60	++	+	0	160/100	+	Healed
F	24	340	90	++	+++	+	250/150	+	Healed
F	25	400	135	++	++	0	170/110	+	Chronic
F	27	400	100	+++	+++	0	240/125	+	
M	32	430	90	++	+++	+	260/120	+	Chronic
F	33	400	140	++	++	0	180/160	+	Chronic
F	37	520	64	+++	+++	0	240/140	+	Healed
M	42	590	115	++	+++	0	160/100	+	Chronic
M	52	580	120	++	+	0	120/100	+	Healed

P. E., productive endarteritis. H. A., hyperplastic arteriosclerosis. N. A., necrotizing arteriolitis.

and a decrease in the number of glomeruli. This decrease in number, however, was apparent rather than actual, and was due to the marked compensatory hyperplasia of the tubules with consequent spreading apart of the glomeruli. The persisting glomeruli were hypertrophied. Some were normal, but many showed varying degrees of alterative glomerulitis.

The vascular changes in the group were similar to those described above. They were moderate in degree in cases with moderate hyper-

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The vascular changes in the group were similar to those described above. They were moderate in degree in cases with moderate hyper-

tension and severe in cases with marked hypertension. In addition, the vascular lesions were always most marked in the scars. Necrotizing arteriolitis occurred in about one-half the cases with severe hypertension combined with uremia and was absent in all cases with moderate hypertension and uremia. About one-half the cases showed chronic pyelonephritis, in the remainder the process was apparently completely healed.

Because of the small size of the kidneys the question naturally arose as to whether we were dealing with congenitally hypoplastic kidneys with a superimposed pyelonephritis. In the autopsy material available in the hospital no case of bilateral congenitally hypoplastic kidneys occurred. There were, however, unilateral examples of this condition. Congenitally defective kidneys may be of three types—agenetic, true hypoplastic and aplastic. We have studied 1 case of agenesis. This occurred in a female, aged 57, whose left kidney was congenitally absent. The ureter was atrophic and thread-like and disappeared in the retroperitoneal fat. The left renal artery was narrowed and became lost in a mass of fatty tissue. The right kidney weighed 180 grams and showed benign nephrosclerosis. The patient died of general peritonitis following a ruptured appendix.

There was 1 case of simple, true hypoplasia. This was in a female, aged 82. The right kidney weighed 120 grams, the left 50 grams. The small kidney was essentially normal in appearance and structure, both grossly and microscopically, except for a slight degree of benign nephrosclerosis. The pelves and ureters of both kidneys were normal. The patient died of bronchopneumonia.

There were four examples of true congenital aplasia. The first was a newborn infant who died 15 minutes after birth. The combined weight of the kidneys was 85 grams. They were joined together at their lower pole. They were markedly irregular in shape and appeared to be formed entirely of small cysts varying from 0.2 to 0.3 cm. in diameter. Grossly no kidney tissue could be distinguished. Microscopically the kidneys were composed of cysts lined with epithelium and intervening bands of connective tissue. No renal tissue was present. The bladder and the ureters were negative.

The second was a 2-day-old infant, who died of peritonitis. Grossly the left kidney was normal in size. The right measured 1.5 cm.

in length and was studded with small cortical cysts filled with clear fluid. Microscopically the left kidney was composed in part of normal renal tissue and in part of connective tissue surrounding cysts lined with cuboidal epithelium and collections of embryonal tubules. The right kidney was made up for the most part of multiple cysts. There were some normal glomeruli and convoluted tubules present but the collecting tubules were poorly developed. Both pelves, the ureters and the bladder were widely dilated.

The third was a male, aged 24. The left kidney weighed 240 grams and grossly and microscopically showed hydronephrosis and acute pyelonephritis. The vessels were essentially negative. The right kidney weighed 5 grams. Grossly it consisted of a small, gray-white mass containing several cysts 0.7 cm in diameter. Microscopically it was made up of a mass of fibrous tissue containing some large tubular structures with a double layer of epithelium, the inner layer being columnar. In addition, there were more normal appearing tubules and these contained colloid casts. No glomeruli were present nor could any vestige of such structures be found. There was also infiltration of lymphocytes, plasma cells and eosinophils in the connective tissue. The blood vessels were fairly numerous and some were of good size. The arteries showed a moderate degree of productive endarteritis and the arterioles a similar degree of hyperplastic arteriosclerosis. The right ureter failed to admit a 1 mm probe at the junction of the pelvis and the bladder. It was small, atrophic and patent for the remainder of its extent, measuring approximately 3 mm in diameter. The patient died of postoperative hemorrhage. The histologic diagnosis of the small kidney was aplasia and pyelonephritis.

The fourth case was a 22 year-old female. The left kidney weighed 200 grams. Microscopically it showed chronic alterative glomerulonephritis. The right kidney was minute in size, measuring 2 by 1 by 0.5 cm. Grossly only traces of kidney substance could be recognized. Microscopically the structure was similar to that in the preceding case and, like it, showed evidence of a healed pyelonephritis. The right renal artery was absent, the origin of the right renal vein could not be definitely identified. The ureter was small at its upper end but increased to normal size after crossing the pelvic brim and approaching the bladder. The clinical diagnoses were chronic glomerulonephritis

and subacute bacterial endocarditis. At autopsy, however, there were found rheumatic heart disease, tuberculous peritonitis, healed bacterial endocarditis and the condition of the kidneys described above. Our interpretation of the condition of the small kidney was aplasia with superimposed pyelonephritis.

From the foregoing cases it can be seen that the congenitally aplastic kidney is readily recognized by the disorderly arrangement of renal structure, the absence of glomeruli and the atypical character of some of the tubular structures. Furthermore, it is obvious that bilateral kidneys of this type are incompatible with life, and hence could not possibly be a factor in the group under discussion. The congenitally hypoplastic kidney is characterized by being merely a small, normal kidney. It is conceivable that if pyelonephritis were superimposed on such a kidney it might be impossible to recognize the underlying hypoplasia. Since, however, in our experience such hypoplastic kidneys have not been found bilaterally, it seems improbable that an underlying hypoplasia of this congenital type could account for the size of the kidneys in the group with bilateral chronic pyelonephritis. It is possible, nevertheless, that in the cases of unilateral pyelonephritis an underlying congenital hypoplasia might have been present. Suggestive evidence for this was the size of the renal artery. In several of our cases the artery to the small kidney was considerably smaller than that to the normal kidney.

The conception that the process in the small kidneys with chronic pyelonephritis represented an infection beginning in childhood rather than congenital aplasia or hypoplasia seemed more plausible. As a result of an infection beginning in early childhood, the combined effects of the resultant scarring and the interference with normal growth could account for the markedly reduced size of the kidneys. A further factor undoubtedly was the changes associated with the uremia present in every case. We refer especially to the alterative glomerulitis.

The occurrence of death at a comparatively early age in this group as a result of renal failure can be explained by the fact that while the small kidneys were competent to take care of the metabolism of the patient during youth, interference with the normal growth of the kidneys prevented them from keeping pace with the increased size of the patient and the increased demand on renal activity or

function The rapidly increasing discrepancy between the size and function of the body and of the kidneys leads finally to uremia in early adult life

This group with unusually small, pyelonephritic kidneys deserves special mention since it is probable that it is this type of renal disease that is associated in some instances with "renal rickets" or "renal dwarfism." In our series, with the exception of a moderate degree of generalized underdevelopment, we had no instance of this disease syndrome in its classical form, but the descriptions given by others fit the type of renal disease found in this younger age group Both Kluge (29) and Fahr (30) have indicated that an underlying focal congenital hypoplasia is important in the etiology of renal rickets Fahr (30) even suggested the term "hypogenetische Nephritis" It is interesting to note that in the past the majority of cases with small kidneys have been diagnosed as chronic glomerulonephritis It may be added, finally, that in rare instances such small kidneys are encountered in the old age group, but they are the combined result of a marked degree of benign nephrosclerosis and pyelonephritis

While chronic pyelonephritis with small kidneys usually terminates in uremia, no close correlation exists between the size of the kidney and its functional capacity The characteristic feature of the renal damage in pyelonephritis is the progressive elimination of functioning nephrons An increasing number of tubules become plugged with casts

THE DIFFERENTIAL MORPHOLOGIC DIAGNOSIS OF PYELONEPHRITIS

Acute pyelonephritis

The following conditions must be considered in the differential diagnosis of acute pyelonephritis

1 *Acute interstitial nephritis* Grossly the kidney is enlarged and may be mottled red and gray or may be pale The capsule strips with ease On section the cortex is thickened Microscopically the characteristic and outstanding lesion is the infiltration of the interstitial tissue with lymphocytes, plasma cells and eosinophils This occurs especially in the cortical region but may extend into the medulla The tubules, especially those which are convoluted, may contain a moderate number of polymorphonuclear leukocytes In addition,

they may show evidence of a healing lesion, as is indicated by the flattened shape of newly formed epithelial cells and the occurrence of mitotic figures in these cells. Abscess formation is not present. This type of nephritis is seen especially in association with streptococcus infections, diphtheria and Weil's disease. Acute interstitial nephritis can be distinguished from pyelonephritis by the minimal number of leukocytes in the tubules and by the absence of both abscess formation and involvement of the pelvis and calyces. This differentiation is, however, not absolute. Indeed, some investigators, notably Putschar (31) and Fahr (30), consider interstitial nephritis as a special form of pyelonephritis.

2 *Diffuse suppurative nephritis* The kidneys may be enlarged and congested and may show focal hemorrhages. Depending on the type of organism, abscess formation may occur, especially in the cortical region. Acute vascular lesions and lesions of the glomeruli are not infrequent and may result in hemorrhages into the capsular spaces and tubules. Such renal lesions are usually associated with the pyogenic cocci, such as staphylococcus and streptococcus. It is often extremely difficult, if not impossible, to differentiate this type of nephritis from pyelonephritis merely by the histologic picture. It may well be but a special type of pyelonephritis. The etiologic agent and the findings in the other organs must be taken into consideration in doubtful cases. The predominance of abscess formation in the cortex, the lack of involvement of the pelvis, the presence of multiple hemorrhages and acute glomerular lesions of the noninvasive type serve to distinguish this condition from pyelonephritis.

Chronic or healed pyelonephritis

Diseases which must be considered in the differential diagnosis of chronic or healed pyelonephritis are as follows:

1 *Chronic glomerulonephritis* Grossly the uniformly finely granular or nodular surface of glomerulonephritis serves in most instances to distinguish it from pyelonephritis, but there are certain cases of pyelonephritis that do have a diffusely nodular rather than a coarsely scarred surface. Histologically the involvement of a large proportion of the glomeruli, the lack of involvement of the pelvis and the absence of colloid casts distinguish glomerulonephritis from pyelonephritis.

2 *Benign nephrosclerosis* Grossly the V-shaped scars, as con-

trasted with the U-shaped scars of pyelonephritis, help to distinguish the two conditions. Microscopically the vascular scars can be distinguished from pyelonephritic scars by the absence of colloid casts, by the character of the interstitial infiltration and by the noninvolvement of the pelvis. The interstitial infiltration in vascular scars is composed of lymphocytes, in pyelonephritic scars, as a rule, lymphocytes, plasma cells and sometimes eosinophils are present. The vascular scars and infiltration are confined to the cortex, while in pyelonephritis they extend into the pyramids and calyces.

3 *Malignant nephrosclerosis* Grossly the surface of the kidney is diffusely nodular. The color varies from a brownish red to a deep red. Petechial hemorrhages often occur beneath the capsule and can also be seen on the cut surface. Microscopically the vessels show the characteristic changes described elsewhere. Some of the tubules may contain polymorphonuclear leukocytes. No abscess formation is present and the interstitial infiltration, while sometimes of a considerable degree, does not approach that seen in pyelonephritis. Colloid casts do not occur.

4 *Hydronephrosis* Grossly the surface of the kidney in hydronephrosis may closely resemble that in healed pyelonephritis, especially if the hydronephrosis is focal. Microscopically the characteristic feature of hydronephrosis is the atrophy of the tubules with the preservation of the majority of the glomeruli. In long-continued hydronephrosis the glomeruli eventually become sclerosed. The interstitial tissue in the cortex has a tendency to a lamellar arrangement, running parallel to the capsule and leading to an apparent separation of the glomeruli. Compensatory dilatation of unaffected tubules does not occur immediately beneath the capsule, as in other forms of renal disease, but in a zone 1 to 2 mm beneath the capsule, the subcapsular tubules being atrophic and distorted. No colloid casts are seen. Infiltration of a small number of leukocytes in the interstitial tissue may occur, but the pelvis is essentially free from such infiltration. No specific vascular changes are present in hydronephrosis. Hyaline arteriosclerosis was found in a few instances in elderly persons. Hypertension was present in only 5 of 22 cases. These were elderly persons, hence the hypertension is to be considered an independent condition.

The signs of inflammation and the absence of colloid casts should

aid in the differential diagnosis of hydronephrosis and pyelonephritis. The two diseases are frequently combined and in such cases the features of both can be recognized. It should be emphasized that renal changes are not always present in hydronephrosis. Thus among 22 cases of hydronephrosis without pyelonephritis there were 14 in which changes in the renal parenchyma were not present.

5 *Congenital hypoplasia* In certain cases one kidney or both kidneys are found to be extremely small and the question arises whether one is dealing with congenital hypoplasia, with childhood pyelonephritis or with a combination of the two. The congenitally hypoplastic kidney occurs in two forms. One is a miniature kidney having all the constituents of the normal kidney. The other type, better termed aplastic, shows a rudimentary structure. Such a kidney may be made up of large tubules, some of which resemble collecting tubules. No glomeruli are present. The tubules and the vessels show no orderly arrangement, but they may be fairly well developed. The substance of such a kidney is largely connective tissue. The ureter may be patent or nonpatent or may be absent. The renal artery of a congenitally aplastic kidney is diminished in size. If pyelonephritis is superimposed, colloid casts are found in the few existing tubules and there is infiltration of lymphocytes and plasma cells in the connective tissue. The vessels in a congenitally aplastic kidney show no change unless there is a superimposed pyelonephritis, in such cases changes occur similar to those described in pyelonephritis alone.

6 *Healed infarcts* The scars of healed infarcts are similar in type to those of pyelonephritis and grossly the two may be confused. Histologically, however, there is rarely any difficulty in distinguishing them. In a healed infarct the most prominent feature is the persistence of the glomeruli as spherical nodules with loss of structure and obliteration of the capsular space. Only a few tubules remain and these are markedly atrophic. Often hemosiderin is present. No infiltration is present in the scar itself although there may be some lymphocytes at the periphery. Any persisting arterioles or arteries show marked narrowing of their lumens due to thickening and hyalinization of their intimas. When stained for elastic tissue, masses of such tissue can be distinguished, these represent blood ves-

sels, of which the other component parts have entirely disappeared. Not infrequently the occluded artery which caused the infarct contains an organized and recanalized thrombus.

DISCUSSION

This study confirms the belief that pyelonephritis is of great significance in clinical medicine. The high frequency of bacterial infection of the kidney becomes evident when one considers that, in our experience, chronic and healed pyelonephritis occurred more frequently than chronic glomerulonephritis. As judged from clinical experience, acute pyelonephritis is the most frequent disease of the kidney. Göppert has aptly characterized pyelitis as a *Volkskrankheit*. Staemmler (32) has pointed out that of the chronic renal diseases associated with "contracted" kidneys only nephrosclerosis is more common than chronic pyelonephritis. The latter is responsible for renal failure more often than chronic glomerulonephritis. Thus in a group of 55 cases with "contracted" kidneys 27 were caused by nephrosclerosis, 18 by pyelonephritis and 10 by glomerulonephritis. In the Boston City Hospital during a 5 year period 272 cases were diagnosed on histologic examination as various types of pyelonephritis and 164 as various types of glomerulonephritis. It is probable that a closer scrutiny of the histologic diagnosis of the latter group, in the light of present knowledge, would result in a decrease in the number of cases of glomerulonephritis in favor of pyelonephritis.

The data here presented confirm the concept that pyuria of renal origin is usually associated with infection and inflammation of both the parenchyma and the pelvis. Except in rare instances, "pyelitis" is a misnomer. In 1934 Putschar (31) stated that "not infrequently behind the clinical picture of pyelitis there is actually a pyelonephritis." In our experience, infection of the renal pelvis without parenchymatous infection occurred in only 1 case. The striking discrepancy between the large number of acute cases and the considerably smaller number of chronic cases of pyelonephritis indicates that acute pyelonephritis ("pyelitis") heals in the majority of instances. The acute infection usually leaves behind small, inconsequential scars. If the infection persists or if it recurs frequently, however, pyelonephritis becomes a disease of grave prognostic significance.

The structural changes in pyelonephritis are quite similar, regardless of whether the disease is hematogenous (descending), urogenous (ascending) or lymphatic in origin. Hence, as pointed out by Putschar (31), the restriction of the term pyelonephritis to the designation of ascending urinary infections, as proposed by Kaufmann and Aschoff, is not tenable. Subclassifications of acute pyelonephritis may be of value from the point of view of the morphologist, but here they are of little practical significance.

The relative degree and extent of inflammation of the interstitial tissue as compared with that of the nephrons, as has been stated, varied from case to case, as well as in the same case at different stages. The seat of infection and inflammation is usually predominantly within the interstitial tissue, including the periglomerular and peritubular lymphatics. We have observed instances of interstitial infection and inflammation without intratubular involvement. The reverse relation was not encountered. The localization of infection and inflammation has an important bearing on the discrepancy between the urinary findings and the symptomatology frequently observed in the course of this disease.

As this investigation dealt mainly with the chronic stage of pyelonephritis and since no systematic bacteriologic examination of the urine was made, adequate data are not available concerning the relative frequency of the causative organisms. The literature indicates that the causative organism varies at different age periods. Thus Putschar (31) stated that *B. coli* are responsible for 90 per cent of the cases in childhood, and staphylococci for from 30 to 40 per cent in aged males. The literature on the rôle of congenital and acquired anatomic lesions in the development of renal infection has been summarized by Haslinger (4) and by Putschar (31). While deformities of the calyces, pelvis and ureter are, in our experience, frequently present, their absence does not preclude the possibility of pyelonephritis. In an appreciable number of instances such deformities were not present. The outflow of the urine was usually not obstructed.

The duration and virulence of the infection and the resulting parenchymatous damage to the nephrons and the arteries, and particularly to the arterioles, determine the clinical manifestations of

the disease in its chronic stages. On the whole, with advancing stages of the disease and with the development of "contracted" and irregularly scarred kidneys local manifestations, such as pain, pyuria, dysuria and bacilluria, tend to disappear, while symptoms of arterial hypertension and renal failure are more apt to appear insidiously. In chronic active cases, however, there may be manifestations of both infection and renal failure. In cases with healed pyelonephritis, if the infection has been diffuse, hypertension and renal failure may develop long after the active infection has subsided. The inflammatory process can presumably, independently of the infection, progressively affect the nephrons and arterioles, resulting in the clinical manifestations described. The difficulty encountered in the diagnosis of healed pyelonephritis has been pointed out. Without an adequate history the diagnosis often cannot be made. The majority of these cases are misdiagnosed as "primary" hypertension, "malignant" hypertension or glomerulonephritis.

The general significance of hyperplastic arteriolosclerosis and productive endarteritis. These vascular changes should be considered as proliferative rather than degenerative lesions. They occur in a variety of conditions, either as a systemic or as a localized vascular response to certain noxious stimuli. Thus they may be present in the lungs as localized lesions in old tuberculous cavities, in areas involved by abscess, in "carcinomatous lymphangitis" or in emphysema. They may also occur in and around gastric and duodenal ulcers. This indicates that infection is not essential for the development of these vascular lesions.

While the presence of vascular lesions in many organs is of no especial clinical significance, their occurrence in the kidney, brain and heart may lead to far-reaching changes. In the kidney these vascular changes are particularly significant because the narrowing of the individual nutrient arteries or arterioles leads to impairment of the nephrons and of renal functions, while the generalized renal ischemia causes severe hypertension. Hence such progressive, obliterative vascular lesions of the kidney represent danger from two *related yet independent* sources. It should be pointed out, however, that unless the decrease in lumen is pronounced, arterial changes without arteriolar changes do not as a rule result in hypertension.

In a previous study we reported the occurrence of pulmonary hyperplastic arteriolosclerosis in patients with advanced mitral stenosis (28). We drew certain analogies between vascular changes in this group and in patients with malignant nephrosclerosis. The clinical, physiologic and morphologic findings indicated a close parallelism between the pulmonary circuit in the group of cases of mitral stenosis and the larger circuit in the group designated as malignant hypertension with malignant nephrosclerosis. In an attempt to explain the etiology of the pulmonary hyperplastic arteriolosclerosis we have presented evidence showing that the combined effect of (1) high arteriolar and capillary pressure, (2) slow blood flow and stagnation and (3) perivascular edema results in such advanced vascular changes. Long-persisting pulmonary edema induced by the prolonged administration of oxygen under high barometric pressure causes similar vascular lesions in the lung of the rat (33). The pulmonary arterial pressure was elevated in these animals (34). We have also referred to observations on animals and on man indicating that hyperplastic arteriolosclerosis in the lungs and in the kidney may develop within as short a period as 2 months. In this connection we wish to point out that advanced hyperplastic renal arteriolosclerosis was noted in a 6-month-old baby with chronic pyelonephritis.

The relation of hyperplastic arteriolosclerosis to local diseases of various organs indicates that under certain conditions chronic inflammation of bacterial as well as of nonbacterial origin is responsible for the development of this vascular lesion. The exact mechanism of the development of the lesion is not known. The effect of proteins or their derivatives in inducing proliferation of tissues is established (34a). It is possible that transudation of such chemical substances into the vascular layers is the factor responsible for setting up proliferative changes. Such physicochemical changes may be localized within a portion of an organ or they may affect more than one organ.

Fahr assumed the presence in malignant nephrosclerosis of a toxin which directly injures the vessel wall and leads to necrosis and inflammatory changes (35). Volhard (36) considered the minute vascular lesions in malignant nephrosclerosis to be the end result of prolonged ischemia due to contraction of the larger arteries. Schürmann and MacMahon (37) claimed that injury to the endothelium

is the primary change. The endothelium constitutes a barrier between the blood and the tissue fluid, and when this is injured substances from the blood may pass into the vessel wall. Schürmann and MacMahon have even postulated that if the endothelial damage is slight the substances may be of fluid nature. If, on the other hand, the damage is great and the endothelium itself is destroyed, cellular elements also may pass into the wall. "The change in the blood is almost immediate coagulation, whereas the change in the wall varies from a mucoid degeneration of the intima to fragmentation and necrosis." While the details of this hypothesis lack evidence, the concept which we have proposed is in general agreement with Schürmann and MacMahon's theory.

The question arises as to the nature of the relation between hyperplastic and hyaline arteriosclerosis. Hyaline arteriosclerosis is the arteriolar counterpart of simple arteriosclerosis and, as has been suggested by Moritz and Oldt (38) and others, is an aging process, the result of "wear and tear" which is accentuated by hypertension. Moritz and Oldt have implied that hyperplastic (proliferative) and hyaline arteriosclerosis do not differ significantly in etiology or in effect. They believe that hyperplastic arteriosclerosis may be an early stage of the hyaline type. Such a concept is not in entire agreement with our findings. We have discovered no or only a slight degree of hyaline degeneration of the hyperplastic arterioles observed in the lungs in mitral stenosis or in the kidney in pyelonephritis. It may be claimed, however, that these patients did not live long enough to develop hyalinization. The most important evidence against the common origin of the two types of arteriosclerosis is the fact that in cases of chronic (benign) nephrosclerosis one does not usually see hyperplastic arteriosclerosis. If the latter were the forerunner of the hyaline type it should be present particularly in patients dying early from causes other than uræmia. Hyaline as well as hyperplastic arteriosclerosis is not rare in severe hypertension (malignant) of long duration. Here the two types are present as manifestations of two independent processes or because the hypertension aggravates the wear and tear. Because of these considerations we believe that hyperplastic arteriosclerosis is not a degenerative response.

Pyelonephritis and hypertension. While hypertension is not pres-

ent in the first attack of acute pyelonephritis, in the chronic and healed stage, as is indicated by the data presented, it is frequently present in its severe form. The association of hypertension with pyelonephritis has been pointed out by few observers. An examination of cases reported in the literature also attests this close correlation. It is only in recent years that specific attention has been called to this phase of the problem. In a study of malignant hypertension and malignant nephrosclerosis we have pointed out that in one group of cases pyelonephritis was present (39, 40). Longcope (41) also noted the frequent presence of hypertension "as one of the late manifestations of the disease." In 11 of 12 cases with hypertension which he studied vascular changes were observed in the retina during life. In the fatal cases, no pronounced or extensive hyaline sclerosis of the arterioles of the kidneys or other organs, such as the pancreas, adrenals and intestines, was observed. In some of the cases a minimal degree of hyaline sclerosis was found. Longcope states that pathologic vascular lesions (presumably referring to hyaline degeneration of the arterioles) are not present. He was unable to correlate the arterial hypertension either with morphologic vascular lesions or with renal insufficiency. Butler (42) discusses 15 patients (6 dead and 9 living) who had chronic pyelonephritis and hypertension for a period of years before there was appreciable diminution in kidney function.

It may be mentioned here that a survey of our cases of malignant hypertension occurring in the Boston City Hospital during the past 4 years indicated that approximately 15 to 20 per cent were on a pyelonephritic basis. In contrast to this, it was found that pyelonephritis was rarely associated with the various types of glomerulonephritis. On the other hand, a large proportion of cases of bilateral congenitally polycystic kidneys were complicated by pyelonephritis and showed the associated vascular changes described above.

Certain clinical features of the hypertension observed in pyelonephritis have characteristics which deserve emphasis. As in other types of severe hypertension, changes in the retinal arterial vessels frequently occur. Pickering (43) reported the association of albuminuric retinitis with high spinal fluid pressures. Such an association also exists in chronic and healed pyelonephritis, as is indicated

by the case reports. Spinal fluid pressures as high as 400 mm H₂O were observed. Cerebral symptoms, such as headaches, throbbing, periodic visual disturbances, confusion, lack of capacity to concentrate, vascular crisis and transient unconsciousness occurred as frequently as in other types of severe hypertension. Thrombosis or hemorrhage of the cerebral arteries, as well as coronary disease, rarely occurred in contrast to other types of malignant nephrosclerosis. Similarly, the degree of cardiac hypertrophy was less severe. MacMahon and Pratt (44) found that the average cardiac weight in a group of 60 patients with malignant nephrosclerosis of undetermined and presumably varied etiology was about 600 grams, while in our group of 38 cases with chronic or healed pyelonephritis and both clinical and histologic evidence of "malignant" vascular changes and hypertension it was about 450 grams. Whether this variation is explained by the difference in the duration of the disease or by the fact that the group with pyelonephritis is younger, cannot be stated. Of 60 patients studied by MacMahon and Pratt, 35 died of uremia, 12 of extensive cerebral hemorrhage, 10 of heart failure, 2 of aortic rupture and others of pneumonia, erysipelas and septicemia. In a group of 38 patients in our series with chronic or healed pyelonephritis and with malignant hypertension on whom adequate clinical and postmortem data were available, 20 died of uremia, 3 of functional left ventricular failure (cardiac asthma) without coronary disease or thrombosis, 3 of rheumatic heart disease, 4 of cerebral encephalopathy (vascular crisis), 1 of meningeal hemorrhage, 2 of dissecting aneurysm, 1 of peritonitis and intestinal infarction as a result of productive endarteritis of the superior mesenteric artery, and 4 of a combination of bronchopneumonia and renal failure. The rarity of organic diseases of the brain and heart differentiates the group having pyelonephritis from both the benign and the malignant group of other etiology. The probable explanation for this difference lies in the fact that the vascular changes in pyelonephritis depend primarily on local inflammatory processes in the kidney and the vessels of other organs remain relatively unaffected. In benign and malignant nephrosclerosis, on the other hand, we are usually dealing with a generalized disease of the arterial and arteriolar systems.

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ent in the first attack of acute pyelonephritis, in the chronic and healed stage, as is indicated by the data presented, it is frequently present in its severe form. The association of hypertension with pyelonephritis has been pointed out by few observers. An examination of cases reported in the literature also attests this close correlation. It is only in recent years that specific attention has been called to this phase of the problem. In a study of malignant hypertension and malignant nephrosclerosis we have pointed out that in one group of cases pyelonephritis was present (39, 40). Longcope (41) also noted the frequent presence of hypertension "as one of the late manifestations of the disease." In 11 of 12 cases with hypertension which he studied vascular changes were observed in the retina during life. In the fatal cases, no pronounced or extensive hyaline sclerosis of the arterioles of the kidneys or other organs, such as the pancreas, adrenals and intestines, was observed. In some of the cases a minimal degree of hyaline sclerosis was found. Longcope states that pathologic vascular lesions (presumably referring to hyaline degeneration of the arterioles) are not present. He was unable to correlate the arterial hypertension either with morphologic vascular lesions or with renal insufficiency. Butler (42) discusses 15 patients (6 dead and 9 living) who had chronic pyelonephritis and hypertension for a period of years before there was appreciable diminution in kidney function.

It may be mentioned here that a survey of our cases of malignant hypertension occurring in the Boston City Hospital during the past 4 years indicated that approximately 15 to 20 per cent were on a pyelonephritic basis. In contrast to this, it was found that pyelonephritis was rarely associated with the various types of glomerulonephritis. On the other hand, a large proportion of cases of bilateral congenitally polycystic kidneys were complicated by pyelonephritis and showed the associated vascular changes described above.

Certain clinical features of the hypertension observed in pyelonephritis have characteristics which deserve emphasis. As in other types of severe hypertension, changes in the retinal arterial vessels frequently occur. Pickering (43) reported the association of albuminuric retinitis with high spinal fluid pressures. Such an association also exists in chronic and healed pyelonephritis, as is indicated

by the case reports. Spinal fluid pressures as high as 400 mm H₂O were observed. Cerebral symptoms, such as headaches, throbbing, periodic visual disturbances, confusion, lack of capacity to concentrate, vascular crisis and transient unconsciousness occurred as frequently as in other types of severe hypertension. Thrombosis or hemorrhage of the cerebral arteries, as well as coronary disease, rarely occurred in contrast to other types of malignant nephrosclerosis. Similarly, the degree of cardiac hypertrophy was less severe. MacMahon and Pratt (44) found that the average cardiac weight in a group of 60 patients with malignant nephrosclerosis of undetermined and presumably varied etiology was about 600 grams, while in our group of 38 cases with chronic or healed pyelonephritis and both clinical and histologic evidence of "malignant" vascular changes and hypertension it was about 450 grams. Whether this variation is explained by the difference in the duration of the disease or by the fact that the group with pyelonephritis is younger, cannot be stated. Of 60 patients studied by MacMahon and Pratt, 35 died of uremia, 12 of extensive cerebral hemorrhage, 10 of heart failure, 2 of aortic rupture and others of pneumonia, erysipelas and septicemia. In a group of 38 patients in our series with chronic or healed pyelonephritis and with malignant hypertension on whom adequate clinical and postmortem data were available, 20 died of uremia, 3 of functional left ventricular failure (cardiac asthma) without coronary disease or thrombosis, 3 of rheumatic heart disease, 4 of cerebral encephalopathy (vascular crisis), 1 of meningeal hemorrhage, 2 of dissecting aneurysm, 1 of peritonitis and intestinal infarction as a result of productive endarteritis of the superior mesenteric artery, and 4 of a combination of bronchopneumonia and renal failure. The rarity of organic diseases of the brain and heart differentiates the group having pyelonephritis from both the benign and the malignant group of other etiology. The probable explanation for this difference lies in the fact that the vascular changes in pyelonephritis depend primarily on local inflammatory processes in the kidney and the vessels of other organs remain relatively unaffected. In benign and malignant nephrosclerosis, on the other hand, we are usually dealing with a generalized disease of the arterial and arteriolar systems.

We have shown that a relation exists between certain types

of vascular changes, i e , hyperplastic arteriolosclerosis and productive endarteritis, on the one hand, and arterial hypertension, on the other. No correlation was found, however, between renal failure and hypertension, a finding which is in agreement with the data presented by Ellis and Evans (23) and by Longcope (41). We have also pointed out that while hyperplastic arteriolosclerosis depends on inflammatory reactions of tissues in pyelonephritis, hyaline arteriolosclerosis, such as occurs in benign nephrosclerosis, is not related directly to inflammation.

We attach special significance to the observation that the vascular lesions in pyelonephritis are different from those in benign nephrosclerosis and are more apt to remain localized in the kidney. They are characterized by proliferative (hyperplastic arteriosclerotic) rather than by degenerative (hyaline) arteriolar changes. From the onset of arterial hypertension, and even before, the vascular changes are identical with those found in malignant nephrosclerosis of any etiology. These changes in pyelonephritis are considered as responses to local tissue inflammation surrounding the vessels. In view of the proliferative character of the vascular lesions affecting the *small* arterioles and because the main site of inflammation is in the interstitial tissue where the renal vessels are located, in diffuse chronic or healed pyelonephritis there is always danger of the development of a pronounced degree of renal ischemia and of severe (malignant) arterial hypertension.

Because of the similarity between changes in pyelonephritis and those occurring in malignant hypertension of other etiology, the study of vascular changes in this condition offers an opportunity, as has been indicated, for the study of the development of vascular changes associated with malignant hypertension. Pyelonephritis is one condition in which we can trace the sequence of events from the onset of the disease to the final stage of vascular changes and arterial hypertension. In contrast, in other types of malignant (fulminating) and in benign (chronic) hypertension the vascular lesions are generalized and the trigger mechanism is not well understood, hence the analysis of causal relationships is difficult.

The study presented indicates that the etiology of vascular changes differs in the so-called benign and malignant types of nephro-

sclerosis As we have suggested elsewhere, malignant nephrosclerosis is usually related to infections or at least to inflammatory reactions of the body (39) This vascular response may be primary or may be superimposed on a preëxisting benign nephrosclerosis Clinical evidence suggests that if the inflammatory vascular process (hyperplastic arteriolosclerosis) is superimposed on a preëxisting benign nephrosclerosis (hyaline degeneration) with hypertension, the progress of the obliterative vascular changes and of the hypertension will be particularly rapid

Because chronic pyelonephritis is a diffuse inflammatory disease of the kidney, the vascular changes are more apt to be localized in the kidney than they are in malignant nephrosclerosis of nonpyelonephritic origin In the latter type we are presumably dealing with a generalized inflammatory disease of the vessels Hypertension develops only if the small arterial vessels of the kidney are *diffusely* affected It is of interest that in a study of hyaline arteriolosclerosis Moritz and Oldt (38) observed the same relative susceptibilities of tissues, with the exception of the kidney, to arteriolosclerosis in hypertensive and in nonhypertensive subjects

From this study no explanation can be offered as to why certain patients respond to pyelonephritis with more severe vascular changes than others Whether a more detailed study of the relation of local tissue changes to the vessels would supply an answer to this question, or whether we have to assume a certain specific individual response by different patients to the same inflammation, cannot be stated

The evidence presented indicates that the hypertension in pyelonephritis depends on obliterative arteriolar lesions of the renal vessels The relation of renal ischemia to hypertension has been advocated by Fahr (35) on the basis of morphologic considerations Goldblatt (45) has clearly demonstrated the close correlation between partial obliteration of the renal arteries and hypertension The considerations here presented suggest that hypertension in pyelonephritis is caused by a similar mechanism, since obliterative vascular lesions exist in the kidney and may be confined to that organ In view of the fact that it has been shown that a severe degree of hypertension of any etiology is always associated with generalized arteriolar resistance (46, 47), this arteriolar resistance in organs

other than the kidney in pyelonephritis is probably caused by humoral or nervous changes. In other types of hypertension than that associated with pyelonephritis such conclusions can be drawn from evidence which is less definite. Nevertheless, in cases with chronic (benign) hypertension, in spite of generalized arteriolosclerosis, Moritz and Oldt found a close correlation between renal arteriolosclerosis and hypertension.

There has been extensive discussion by several writers as to whether the separation of benign (chronic) and malignant (acute) hypertension is justified. Arterial hypertension is, at least in some clinical types, a response to renal ischemia. In hyaline arteriolosclerosis the ischemia, as indicated by the width of the lumens, tends to be less severe and less progressive than in the malignant type. We have also presented some evidence that the etiology of the two types of sclerosis is different. Hence, both from a prognostic and from an etiologic point of view, a separation is justified. One must realize, on the other hand, that the clinical features of the two syndromes may, at least for some time during the clinical course, be similar. Hence the diagnosis of malignant hypertension or nephrosclerosis is often made in retrospect.

Pyelonephritis and stones Several of the patients with chronic pyelonephritis had renal, pelvic or ureteral stones. It is known that "primary" stone, like any other type of obstruction, predisposes to pyelonephritis (4). Contrariwise, stones may develop as a result of pyelonephritis, particularly of staphylococcic origin. In such cases, as has been shown by Hellstrom (48), all layers of the stone contain clumps of staphylococci, indicating that the infection was primary and the stone formation secondary.

Pyelonephritis and toxemia of pregnancy The relation of low kidney reserve and arterial hypertension of various etiology to toxemia of pregnancy is recognized. Obviously, toxemia of pregnancy includes a number of unrelated complications of pregnancy (49). Our data do not permit an estimation of the rôle and incidence of pyelonephritis in toxemias of pregnancy. It is of interest that in the group of patients with small pyelonephritic kidneys, out of 8 with a history of pregnancy 6 had repeated attacks of toxemia. In several instances the toxemia developed before permanent hyper-

tension An example of such a case is given in Charts 5 and 5A In none of the cases which we studied did fatal toxemia occur in association with pyelonephritis In our experience acute pyelonephritis per se is not responsible for toxemia unless we are dealing

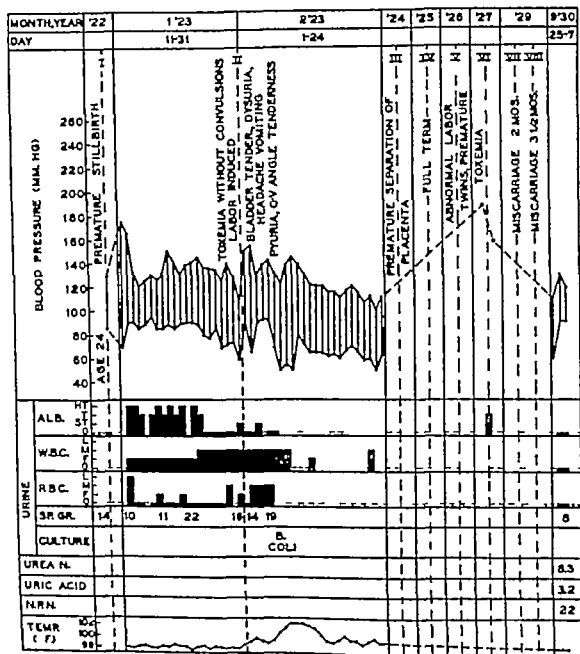


CHART 5 FEATURES OF CLINICAL COURSE IN A YOUNG FEMALE PATIENT WITH REPEATED TOXEMIAS OF PREGNANCY

Chart illustrates the development of severe ("malignant") hypertension

with the recurrent "acute and healed" type of disease Of 320 patients with toxemia Peters (50) found that 13 per cent suffered at one time or another from conditions included under the terms pyelitis and pyelonephritis It should be pointed out that recognition of latent kidney disease in cases with toxemia and with chronic

pyelonephritis may be particularly difficult because of the absence of specific urinary findings such as exist in glomerulonephritis

Pyelonephritis and Bright's disease Bright in his original paper (51) described a disease of varied etiology leading to renal failure

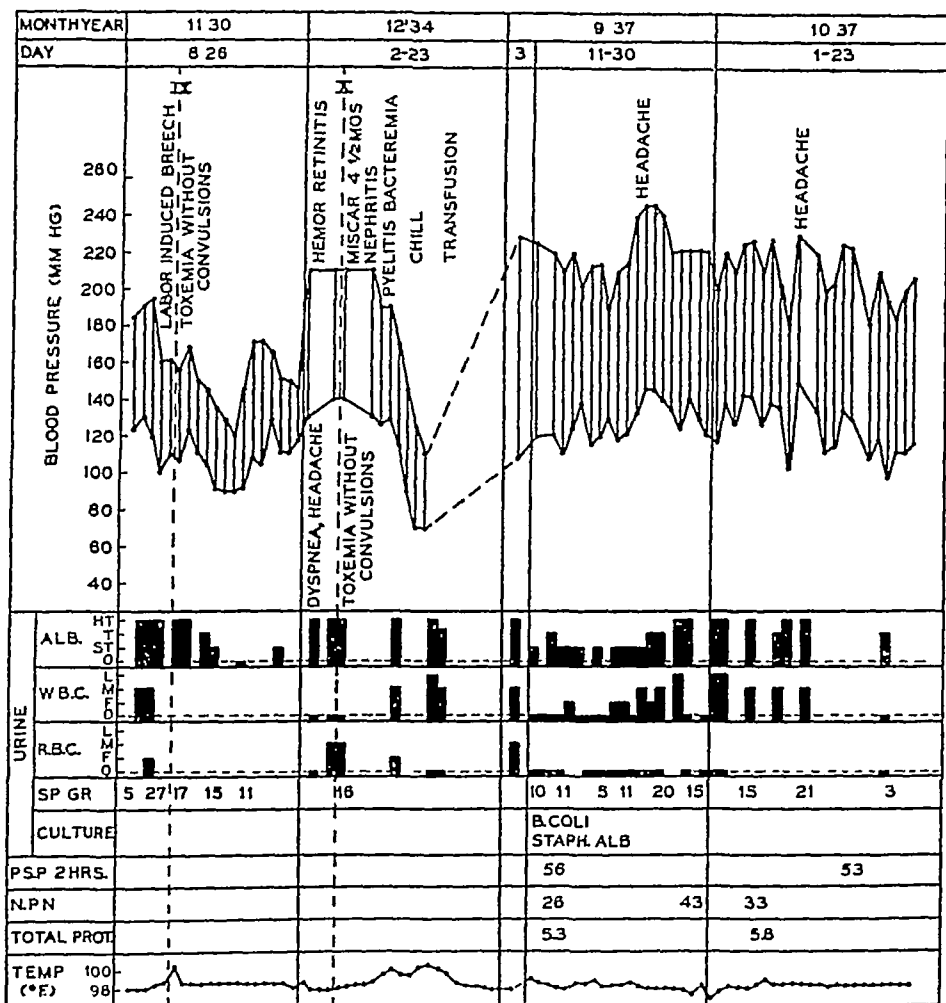


CHART 5A CONTINUATION OF CHART 5

In the century following his great contribution important advances have been made in classifications of renal disease. The classifications proposed are somewhat arbitrary, as they usually fail to emphasize the interrelation between the various types of Bright's disease. Indeed, pyelonephritis is not considered as a form of

Bright's disease (36, 52, 53, 54) The arbitrary separation of kidney diseases into "medical" and "surgical" types has also delayed progress. The fact that pyelonephritis can lead to renal failure, vascular lesions, and arterial hypertension long after the disappearance of bacterial infection indicates that it should be considered as one form of Bright's disease.

Infection, exogenous and endogenous substances and the aging processes can affect various portions of the nephrons or vascular elements in various combinations. Depending on the specific localization of the functional or structural damage, various groups of renal diseases are separated with justification. For obvious reasons cases with combined renal diseases are more common than those with a single type of pathology. The collective term Bright's disease is therefore still useful to remind physicians of the interrelation between these groups.

SUMMARY AND CONCLUSIONS

1 The natural history of pyelonephritis was studied in 100 selected cases with necropsies and also in selected clinical cases. The material studied did not include cases with focal pyelonephritis of no clinical significance.

2 The clinical course of pyelonephritis is strikingly variable. The renal infection often heals in a short time, although it may persist for years or for decades, during which activity may be continuous or recurrent.

3 Pyelitis practically never exists unaccompanied by pyelonephritis.

4 Pyelonephritis has been classified as (a) acute, (b) chronic (active), (c) healed, (d) healed and recurrent. The structural and clinical characteristics of the various types or stages have been defined and it has been emphasized that clinically, the sharp separation of the various stages is often difficult.

5 The structural characteristics of pyelonephritis are essentially the same regardless of whether the infection is hematogenous (descending), urogenous (ascending) or lymphatic in origin. In all types marked changes occur in the renal lymphatic system as well as in the nephrons.

6 In chronic and healed pyelonephritis the main morphologic characteristics consist in (a) inflammatory reaction of the interstitial tissues, (b) colloid casts in the tubules, which are lined with atrophic epithelium, (c) periglomerular fibrosis, (d) evidence of infection or inflammation within the tubules

7 A description has been given of the morphologic characteristics of various stages of pyelonephritis which serve to differentiate it from acute interstitial nephritis, diffuse suppurative nephritis, glomerulonephritis, "benign" and "malignant" nephrosclerosis, hydronephrosis, congenital hypoplasia and aplasia and healed infarcts

8 The functional capacity of the kidney often shows a considerable degree of fluctuation during the course of pyelonephritis

9 Pyelonephritis, particularly in the chronic and the healed stages, is often associated with arterial hypertension. This hypertension may be present with normal, adequate or poor function of the kidney. The hypertension of pyelonephritis is often severe and is frequently accompanied by nervous symptoms, including cerebral encephalopathy, neuroretinitis and high cerebrospinal pressure, and by toxemia of pregnancy. The syndrome of left ventricular failure with attacks of cardiac asthma was frequently observed. Organic diseases of the cerebral and coronary vessels, in contrast to chronic hypertension and to "malignant" nephrosclerosis of other origin, are rare. The hypertension of pyelonephritis can be independent of the activity of renal infection. It often advances when the disease is in the healed stage.

10 Vascular changes frequently occur in pyelonephritis, particularly during the chronic and the healed stages. Acute arteritis or arteriolitis, resembling lesions in periarteritis nodosa, phlebitis, hyperplastic arteriosclerosis, productive endarteritis and necrotizing arteriolitis are the types of lesions which are related to the renal infection.

11 A relation was found between the severity and diffuseness of the vascular lesions, on the one hand, and arterial hypertension, on the other hand. Cases with severe hypertension had advanced hyperplastic arteriosclerosis, a certain type of productive endarteritis and necrotizing arteriolitis.

12 The correlation between the size and the functional capacity of the kidneys and hypertension was not so close as the correlation between vascular changes and hypertension

13 Vascular changes and hypertension did not occur in the group of cases with renal tuberculosis and hydronephrosis *uncomplicated* by pyelonephritis

14 The relationship between hyperplastic and hyaline types of arteriosclerosis has been investigated

15 Evidence is presented which indicates that the inflammatory renal process and the intravascular pressure are responsible for the arterial lesions described

16 In unilateral pyelonephritis, particularly in cases without severe hypertension, the vascular lesions are confined to the affected side. Unilateral pyelonephritis with advanced vascular changes, regardless of the size of the kidney, may or may not be associated with hypertension

17 Because the vascular lesions in pyelonephritis are similar to the severe obliterative vascular lesions found in malignant nephrosclerosis, there is a great tendency to severe hypertension in patients with pyelonephritis

18 It is estimated that pyelonephritis is responsible for at least 15 to 20 per cent of cases of malignant hypertension

19 The vascular lesions in chronic pyelonephritis are restricted mainly to the kidneys, in contrast to those in "primary" malignant hypertension, which are generalized

20 Polycystic kidneys, hydronephrosis and renal tuberculosis were often found complicated by pyelonephritis. Glomerulonephritis and pyelonephritis, in our experience, seldom coexisted

21 Alternative glomerulitis was found in cases with terminal uremia. This type of glomerular lesion should be differentiated from that found in glomerulonephritis

22 The "contracted" kidney of pyelonephritis (renal rickets type) is related to infection in childhood and interference with growth, rather than to congenitally hypoplastic or aplastic kidneys. This type of pyelonephritis is apt to predispose to one form of toxemia of pregnancy

23 The importance of the study of the arterial hypertension of

pyelonephritis lies in the fact that the sequence of events from the initial renal infection to the terminal stage of severe hypertension can be traced fairly clearly. This type of hypertension is considered to be of renal origin (Goldblatt)

24 Pyelonephritis in the chronic and the healed stages should be considered as one type of Bright's disease in which infection and inflammation affect both the vessels and the nephrons. The vascular and the renal functional damage are related to the same cause, but they may be independent of each other.

25 Chronic and healed pyelonephritis occurs more frequently than chronic glomerulonephritis.

26 Pyelonephritis is a disease of importance in obstetrics, pediatrics, internal medicine and surgery and is one renal disease which can be treated effectively in its incipient stage.

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DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION AND THE ASSOCIATED RETINAL LESIONS¹

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INTRODUCTION

Any elevation of systemic blood pressure is probably accompanied by a rise of blood pressure in the retinal arterial system. This rise in retinal intra-arterial pressure may or may not be proportional to the rise of pressure in the brachial arteries under varying conditions, as was demonstrated by the research of Baillart, whose studies with the ophthalmodynamometer have been of great value from both the physiologic and clinical standpoints. Elevation of the systemic, and presumably then of the retinal, blood pressure is usually, but not always, associated with structural changes in the retina or its vessels which can be recognized by ordinary ophthalmoscopic methods. Therefore, careful examinations of the retinas of persons with elevated blood pressure can be of considerable value in differentiating various types of systemic disease in which an elevation of blood pressure occurs and in estimating the amount of associated organic change, particularly in the arterioles. If it can be assumed, as seems logical, that the visible reactions in the retinal vessels are similar, though at times disproportionate, to the invisible reactions taking place in vessels of similar size throughout the body, it is obvious that an explanation of the mechanism of these reactions in the retina will go far toward solving the mechanism of diffuse vascular disease. This phase of ophthalmoscopy is of particular interest to the internist.

¹The authors have revised and extended a report which appeared in the Transactions of the Fifteenth International Congress of Ophthalmology, Cairo, Egypt, 1937.

It is the main purpose of this communication to summarize so far as possible our knowledge of the general features of hypertensive, vascular renal disease and the basic principles involved in the origin of the disease and in the initiation of its retinal complications, the serious nature of which from a general prognostic standpoint has long been recognized

HISTORICAL RÉSUMÉ

The first use of manometers for measuring blood pressure (1733) is attributed to Stephen Hales, an English clergyman, and the first practical instrument for estimating the blood pressure was devised by von Basch (24, 25) in 1880. The type of sphygmomanometer now in use was invented by Riva-Rocci in 1896, and independently in 1897 by Hill and Barnard. It was not until after 1910, however, that sphygmomanometers were very generally used by practicing physicians, and most of the voluminous literature on hypertension as a clinical entity dates from that time.

In speaking of the relation of cardiac hypertrophy to renal disease, Richard Bright expressed the belief that hypertrophy of the heart must be attributed to increased work performed by that organ. The two most logical explanations for this increased work were, he thought, "either that the altered quality of the blood affords unwonted stimulus to that organ immediately, or that it so affects the minute and capillary circulation as to render greater action necessary to force the blood through the distant subdivisions of the vascular system." Following the work of Bright, the presence of an increased blood pressure in certain patients with albuminuria was recognized by an increased tension or lessened compressibility of the radial pulse to palpation and later by sphygmographic studies. The hypertension was considered to be invariably a consequence of preexisting renal disease or of arteriosclerosis.

George Johnson, in 1868, was one of the first to suggest that there was present in Bright's disease a vascular factor in addition to the renal lesion. He called attention to Bright's suggestion as to the etiology of the cardiac hypertrophy in chronic renal disease. He also quoted Sanderson as saying in the "Handbook of the Sphygmograph" that, "In cases of chronic Bright's disease with hypertrophy of the left

ventricle, the sphygmograph affords decided evidence of increased arterial pressure." Of his own studies, Johnson stated "In every fatal case of chronic Bright's disease with hypertrophy of the left ventricle there has been decided hypertrophy of the arterial walls in most of the tissues examined, not only in the kidneys, but also in the skin, the intestines, the muscles, and the pia mater", and, "The facts hitherto observed all point to the conclusion that hypertrophy of the walls of the small arteries is a result of their continued overaction in opposition to the heart." Evidently, however, he regarded the kidney as the primary source of the difficulty, for he said "In proportion to the destruction of the renal gland cells and the consequent diminution of the secretory power of the kidney, there is less demand for blood to be acted upon by the gland, the small arteries consequently contract upon their contents so as to maintain the balance between the blood supply and the diminished secretory action of the kidney. This continued overaction of the small arteries in antagonism to the heart results in hypertrophy of their muscular walls."

A few years later (in 1872), Gull and Sutton expressed the opinion that a "hyalin fibroid change" in the minute arteries, arterioles and capillaries of various tissues was the primary and essential phenomenon in cases of chronic Bright's disease with contracted kidneys. They stated that this degeneration of the blood vessels commonly began in the kidneys, but that it might begin in other organs, so that hypertrophy of the heart with degeneration of the blood vessels might be found associated with healthy kidneys. The contraction and atrophy of the kidneys usually present were considered by them to be "only part and parcel of the general morbid change." They suggested the name "arterio-capillary fibrosis" for the disease entity.

About thirty years later, in 1904, Jores interpreted the vascular lesions in nephritis in a different manner than either Johnson or Gull and Sutton. He did not deny that the muscularis of the arterial walls could hypertrophy in nephritis, but he contended that the hypertrophy was not a specific or dominant change in the small arteries in cases of contracted kidney. Jores believed that the lesion commonly seen in the small arteries in cases of nephritis was a "pure" arteriosclerosis characterized by fatty degeneration of the intima. This lesion of the small arteries was found not only in the kidneys

may arise also "in primary irritability of the vasoconstricting mechanism from unknown, probably extrarenal causes, which lead eventually to arteriolar sclerosis "

Probably the most valuable contributions of more recent years have been those of Volhard (236, 238), whose classification of the various forms of nephritis has been almost universally accepted at the present time. He divided the bilateral hematogenous renal diseases into two main groups. In the first group no circulatory disturbance is present in the kidney. This group includes principally the nephroses and focal nephritides. The second group, with which we are particularly concerned, includes those cases in which there is a disturbance of circulation in the kidneys. To this group belong diffuse glomerulonephritis and nephrosclerosis. In acute glomerulonephritis Volhard postulated an angiospastic contraction of the renal vessels (237), in chronic glomerulonephritis, he assumed that there was an organic disturbance of circulation in the glomerular capillaries and renal vessels, with a resultant generalized contraction of the systemic arteries and a consequent rise in blood pressure. The end result of this condition is the secondary contracted kidney. In nephrosclerosis, the primary condition is essential hypertension and the end-stage the primary or genuine contracted kidney. Volhard (236, 238) has further subdivided nephrosclerosis into the benign and malignant types. Benign nephrosclerosis is associated with his "red hypertension" in which angiospastic features are absent. This disease, according to Volhard, is essentially arterial, there is a weakening of the muscular coats of the arteries with hyperplasia of the elastica. Malignant nephrosclerosis is associated with angiospastic or "pale" hypertension. In the earlier stages of this disease, which is essentially arteriolar, hypertrophy of the muscles in the walls of the smaller arteries and arterioles results from the persistent constriction. In the terminal phases necrosis of the smallest arteries and arterioles in the kidneys is the characteristic lesion. Volhard would seem to be the first to stress the importance of angiospasm, particularly of the arterioles, in hypertensive disease, although the presence of arterial constriction had been recognized or suspected as previously noted.

Considerable discussion has centered on the question whether arteries or arterioles can remain for as long a period of time in a con-

dition of spasm as would be necessitated by Volhard's assumptions concerning the pathogenesis of hypertension. Pal's views on this subject are of considerable interest. He stated that there are three causes of arterial narrowing: (1) excitation of the vasoconstrictors or direct stimulation of the fibrils, (2) transition of the interstitial tissue into the position of rest as a result of loss of blood or injury, as in active narrowing or collapse and (3) acute elevation of tone in the muscle of the arterial wall, a tonic stimulus. Pal thought that spasm occurs only in the event of acute stimulation of the kinetic nerves or of the contractile fibrils directly, or else, perhaps, as a result of irritation of the intima as by small emboli. Active narrowings of the arterial wall proceed from the vasoconstrictors and consume energy material. These are maximal spasms. If the kinetic stimulus ceases, the hypertonic state and the position of the arterial wall may remain the same as far as it can resist the blood pressure. This condition does not demand the consumption of energy. A new kinetic stimulus can again induce spasm. In acute glomerulonephritis, according to Pal, narrow hypertensive arteries are present several days before the appearance of changes in the urine. They are not caused by the nephritis and can be seen also in infections, lead poisoning and eclampsia. In these diseases, because of vessel irritability, angiospasms—pressor crises—may occur. They do not necessarily close the vessels. But these spasms are not present in the contracted arteries of the rest stage, between pressor crises. A continuous spasm, Pal said, is contradictory to biologic experiences with smooth muscles, and also to histologic studies. The general narrowing of the arteries in "pale" hypertension and in nephritis is not due to vessel spasm, as Volhard thought, but to a continuous hypertonus, what Sherrington terms in muscle "the postural activity." The narrowing of the arteries is not due to a kinetic stimulus but to a rapid increase of tone resulting from changes in cellular metabolism of the arterial wall.

Pal's interpretation of the nature of the arterial narrowing may fit in with a recent French conception of the nature of hypertension. Dumas suggested that arterial hypertension is a diathesis originating in a modification of the blood serum similar to that seen in hypercholesterolemia, hypercalcemia, variations in protein equilibrium, and the like. These humoral difficulties, he thought, are probably the

result of lesions of the endocrine organs or of the viscera, such as are seen in the majority of diseases of nutrition, and are not related exclusively to renal disease. Dumas stated that there is no doubt that the vascular lesions are the result of the hypertensive state. Loss of elasticity and of permeability of the capillaries and arterioles are to be regarded histologically as the very early or commencing stage of arterial hypertension.

Dumas divided essential hypertension into three phases. In the first or silent phase the patient is essentially symptomless. In the second or established phase, the disease has become organic and visceral lesions are present. Cerebral hemorrhages, cardiac failure or uremia may terminate this phase. It is possible, however, for the hypertension to pass into the third or involutional phase, in which the blood pressure drops and arteriosclerosis dominates the picture—the hypotensive stage of hypertension. According to Bonamour, the retinal changes in Dumas' first phase are spastic in type. The blood pressure in the central artery of the retina is likely to be elevated disproportionately to the blood pressure in the brachial arteries. Patients may complain of transient loss of vision. Post-spastic thrombosis of the central artery may result in permanent loss of vision. In the second or established phase, retinitis develops in cases which are running a rapidly progressive course. If the disease progresses more slowly, sclerosis develops in the retinal arteries as a defense reaction. In the third or involutional phase, the sclerosis in the retinal arteries is likely to be quite marked, and lesions such as arteriosclerotic retinitis and retinitis circinata are characteristic. In Bonamour's opinion, retinitis of the hypertensive type is essentially vasospastic in origin. As a result of arteriolar constriction, reactional dilatation and stasis develop in the capillary bed and serous and hemorrhagic transudations take place into the retina.

From the purely clinical standpoint, at least, and possibly also from the histologic standpoint, Volhard's conception of angiospasm with subsequent organic changes seems to explain better than any other theory the modes of participation of the retina in hypertensive disease and in nephritis. In these diseases an essentially similar end-stage may be reached through varying primary modes of development. It would seem logical to assume that the same basic processes are

concerned in the production of the retinal as of the renal complications. Probably, then, the differentiation between the retinal lesions in hypertension and in nephritis lies, not in the terminal histologic picture, but in the order of development of the different factors eventuating in this terminal picture. Detailed studies of the retinal lesions in these vascular diseases have been stimulated considerably by the desire of internists for aid in differentiating the various systemic diseases included in this group. In the main, the position of the ophthalmologist up to the present time has been essentially that of Leslie Paton, as quoted by Allbutt in 1915: "I certainly do think that clinically the three types (i.e., of renal disease, of hyperpiesis, and of senile atherosclerosis) are distinct, but whether ophthalmoscopically one can always distinguish between them is another question." In the senile form of arteriosclerosis, "the edema changes are but little seen and the degeneration is probably mainly due to deficient nutrition." To distinguish between the other two forms (nephritis and arteriosclerosis with high tension) would require almost a treatise. It is to be hoped that, in the future, if clear conceptions can be obtained of the sequence of events in the genesis of the retinal lesions, the problems of differential diagnosis will not appear so hopeless.

This problem of the pathogenesis of "albuminuric retinitis" has been a consuming one almost since the beginnings of our knowledge of albuminuria as an expression of disease of the kidneys. Bright himself recognized that loss of vision was a symptom in cases of certain patients with albuminuria. The cause of this loss of vision was unknown. Against the supposed cerebral origin of the blindness Türck was able, in 1850, to present anatomic evidence of a lesion in the retina, and the argument between uremic amaurosis and retinitis was on. With the increasing use of the ophthalmoscope it soon became evident that, while uremic amaurosis does occur, the lesion is in the majority of cases an organic retinal one.

Probably the first report on the observation of retinitis in nephritis is that of von Graefe in 1855. He described, in a case of Bright's disease during the puerperium, very widespread white exudative plaques in the retina with an extensive detachment of the lower retina. Several months later the retina was found to be reattached, but the vessels in the affected area seemed to be in large part obliterated.

The white plaques had also completely disappeared. Evidently von Graefe had seen retinitis in nephritis before this time, for he stated that he had never before observed healing of the retinitis in Bright's disease. In 1856, Heymann (110) reported the observation of ophthalmoscopic changes in several cases of Bright's disease. He considered that the changes were due to fatty degeneration of the retina, and that they could be found not only in diseases of the kidney, but also in diseases of the brain and of the heart and also in other constitutional troubles such as marasmus. He thought that the amaurosis of Bright's disease was due to cerebral changes with serous exudation into the brain and retina. The first detailed description of "albuminuric retinitis" was published by Liebreich in 1859. He mentioned narrow arteries, full and tortuous veins, edema of the disk and retina, hemorrhages, punctate exudates, and the larger grayish-white lesions which we now speak of as "cotton-wool patches." These changes he did not consider pathognomonic of Bright's disease, but snowbank and macular star exudates were, he believed, pathognomonic of renal disease.

Not much has been added to the gross ophthalmoscopic picture of "albuminuric retinitis" since Liebreich's description. The main interest has centered upon the general and local pathogenesis of the retinal lesion. In 1860, von Graefe and Schweigger reported a case in which retinitis developed shortly after two attacks of transient loss of vision without retinal findings but associated with "uremic" convulsions. This case is quite similar to one reported by us as an acute vasospastic hypertension, and rather supports the theory of the angiospastic origin of the retinitis. It was not so interpreted by von Graefe and Schweigger, however. They thought that the retinitis was the result of nitrogenous products in the blood, and was never a prodromal but always a terminal symptom of Bright's disease with contracted kidney, even in cases without albumin in the urine and without edema.

In discussing the general pathogenesis of "the retinitis associated with albuminuria," Allbutt wrote in 1871: "The retinitis never precedes nephritic degeneration, as Laudouzy supposed, yet so silently may shrinking of the kidney go on, that enfeeblement of sight may not infrequently be the first symptom which leads the sufferer to a doctor,

and the doctor, who begins by examining the eyes for spectacles, ends by discovering interstitial nephritis. Indeed, the retinitis so far from being a forerunning symptom, would seem from my experience to be an evidence rather of decided or advanced disease, and would lead me to give a very unfavorable general prognosis." And further, "But common as arterial degeneration is in advancing life, I have never yet heard of this condition, apart from the granular kidney, being accompanied by the form of retinitis called albuminuric."

This statement is quoted at length because it expresses so well the attitude of essentially all ophthalmologists and internists for at least the following fifty years, and of many, especially of the English, ophthalmologists, even today. Most internists at present agree that a retinitis of "albuminuric type" can occur in cases in which no evidence of renal insufficiency can be demonstrated clinically (260), and in which, at necropsy, the kidneys show no evidence of primary nephritis. In 1924 we (242) reported a group of fourteen cases, with marked hypertension, adequate renal function and neuroretinitis, and said "In such cases it seems more reasonable to assume that the retinitis is dependent on the hypertensive vascular disease, rather than on a primary lesion of the kidney." Since that time, this opinion has been supported by our further clinical, biopsy, and pathologic studies, in association especially with Kernohan and Barker (134, 135), and it has been confirmed by workers elsewhere, notably by Murphy and Grill (269), Scott, Seecof and Hill, Pilcher and Schwab (195, 196), Ellis (66) and by Moritz and Oldt.

In 1925, Kahler and Sallmann expressed the belief that patients with essential hypertension and completely intact renal function can present a typical "nephritic neuroretinitis." They quoted experiments of Heidenhain and von Basch which showed that electrical stimulation of centers in the medulla would cause generalized vasoconstriction. They classified essential hypertension as (1) central, (2) peripheral toxic, and (3) anatomic. They found retinitis only in cases of "central toxic hypertension" and thought that the retinitis in glomerulonephritis was dependent on an associated or secondary "central toxic" hypertension. Kahler studied the effect of lumbar puncture in sixty-four cases of essential hypertension with normal renal function. He found a drop of blood pressure averaging 50 mm

of mercury following a puncture in a third of the cases. He thought that the drop of blood pressure occurred in cases of hypertension of central toxic origin and not in those of peripheral origin. A drop of 40 to 50 mm of mercury in blood pressure after spinal puncture in cases of hypertension, with relief of headache and other disagreeable symptoms, was noted by Bailliart, Magniel and Saragea in a group of twenty-two cases in 1924. In seventy-three patients with normal blood pressure and in six with benign hypertension, Messick noted an initial rise of 5 to 30 mm of mercury in systolic pressure following spinal puncture. In eight cases of malignant hypertension, an initial fall of 10 to 25 mm of mercury in the systolic pressure occurred in five.

Two main theories of the local pathogenesis of "albuminuric retinitis" have been proposed, the toxic and the vascular or circulatory theory. Neither theory has clear precedence in time. Von Graefe and Schweigger, in 1860, stated their opinion that the retinitis was due to the toxic action of nitrogenous waste products in the blood. This theory has been supported and elaborated by Opin and Rochen-Duvigneaud, Widal, Morax and Weill, and by Leber. Chauffard, Laroche and Grigaut thought that the toxic agent was cholesterin. The most recent work on the toxic theory of "albuminuric retinitis" has been done by Koyanagi. The conception that retinitis in nephritis is due to a disturbance of circulation was first advanced by Traube in 1859. He thought that it might be caused by a secondary increase of tension in the aortic system. In 1887, Herzog Karl published an elaborate monograph on the thesis that "albuminuric retinitis" was the result of organic sclerotic changes in the vessels of the retina. This view was supported by von Michel. The latter wrote, in 1899 "The ophthalmoscopic picture of the so-called albuminuric retinitis is—as I have earlier stated—only the expression of a disturbance of the circulation and tissue lesions of the retina brought about by a primary disease of the vascular system of the central retinal artery and vein in the form of an arterio- and phlebo-sclerosis with their resulting lesions." This theory did not gain very wide credence because it was possible to find histologically, as was shown notably by Schieck (215) and by Cohen, cases of "albuminuric retinitis" without demonstrable lesions in the retinal vessels. It was further supported by Jores' contribution in 1904. He stated

that "albuminuric retinitis" occurred only in those cases of nephritis in which arteriosclerosis was present in many of the other organs and tissues of the body, and he believed that the lesions in the retinal vessels were a part of this diffuse "pure" arteriosclerosis. In 1927, Verwey was able to demonstrate, by fat stains, in all cases of "albuminuric retinitis" examined, a hyaline lipoid degeneration of the walls of the small terminal arterioles of the retina. This work was confirmed by Friedenwald who was "convinced that albuminuric



FIG. 1. RETINA AT NECROPSY.

Case of Dr. J. S. Friedenwald. Flat preparation of retina (not a section) stained with Sudan III showing hyaline lipoid thickening of walls of small arterioles.

retinitis is in essence a complication of retinal arteriolar sclerosis" (figs. 1 and 2).

The most logical explanation of the mode of origin of "albuminuric retinitis" seems to be that of Volhard, (216, 237) who regarded both the arteriolar sclerosis of Verwey and the retinitis as a result of ischemia due to spasm in the larger arterioles. Volhard's conception of ischemic or angiospastic retinitis seems to be more generally applicable than any other to the retinal complications of hypertension and nephritis and to permit of more ready comparison of these complica-

tions with the other features of the systemic disease. A possible link in the transition from angiospasm to sclerosis and retinitis is furnished by Friedenwald, who suggested that, because of the sensitivity of the retina to lack of oxygen, the anoxemia resulting from angiospasm may cause the liberation of tissue lysins which initiate the degeneration of the walls of the arterioles. Kyrleis also con-



FIG 2 RETINA AT NECROPSY

Case of Dr J S Friedenwald showing terminal arteriole in retina completely obstructed by hyaline lipid thickening of its wall and an associated cotton-wool patch (Flat preparation of retina stained with sudan III)

firmed the findings of Verwey with regard to the presence of arteriosclerosis in "albuminuric retinitis". However, he did not think that this arteriosclerosis could be made responsible for the retinitis because the arteriolar lesions were not sufficiently widespread, were not consistently related to the local retinal lesions, were more marked in the optic disks where exudation and hemorrhage did not occur, and were not parallel in grade to the severity of the retinal changes

It is to be noted, however, that Friedenwald, by the use of flat preparations of the retina, was able to demonstrate that the arteriolosclerosis was much more widespread in the retina than would be apparent in the cross sections studied by Verwey, and Kyrleis noted that the larger arteries in his sections showed a medial thickening of variable degree, which in his opinion implied a general narrowing of the arterial system. Kyrleis agreed with Volhard that "albuminuric retinitis" is a result of a disturbance of circulation, but he did not agree that it is of ischemic type. He found capillaries engorged rather than empty. In his opinion, therefore, the retinal lesions are due to increased permeability of the capillary walls resulting from the abnormal chemical and biologic character of the relatively stagnant capillary blood.

The study of the retinal vessels in the absence of retinitis as an aid in the diagnosis of systemic disease seems to have begun with Gowers. In 1876, he wrote "When in chronic Bright's disease, the pulse is incompressible, there may as a rule be seen reduction in size of the retinal arteries independently of any retinal disease, and this reduction in size is fairly proportionate to the increased arterial tension." He thought that the reduction in size was due to contraction of the vessels. He said further "When the retina is free from local disease, there is no reason to believe that the retinal artery and vein differ in their condition from other arteries and veins of the same size, and, therefore, any marked change in their state apart from cerebral or ocular disease may be taken as evidence of a similar change throughout the vascular system." And again "There is, of course, nothing new in the fact that the retinal arteries are small in Bright's disease, it has long been remarked as a common feature in albuminuric retinitis but it is usually regarded as a consequence of the retinal change, and the points on which I would insist are that it occurs also quite independently of the retinal change and stands commonly in direct relation to another condition, the blood tension."

In essence, these statements cover the recognized significance of retinal vascular lesions in systemic disease today. Elaborations of the ophthalmoscopic signs of arteriosclerosis and of the relationship of the retinal lesions to general vascular disease were made by Rachlmann in 1889, by Gunn in 1898, by Rohmer in 1906, and by numerous others.

since that time The conception of retinal arteriosclerosis as a part of general and cerebral arteriosclerosis grew, and it has been only in comparatively recent years that it has become increasingly apparent that the lesions observed ophthalmoscopically in the retinal arterial branches are really arteriolosclerotic in their characteristics and systemic significations The publication of O'Hare and Walker in 1924 (175) forced attention to the fact that, almost without exception, so-called retinal arteriosclerosis is a part of hypertensive disease and diffuse arteriolosclerosis and not of atherosclerosis

One statement of Gunn's (97, 98) is of particular interest with reference to the Volhard theory of angiospastic sclerosis and retinitis He thought that a narrowing of the arteries together with an abnormal rigidity of their walls diminished the rapidity of the blood stream in the capillaries and veins with a resultant tendency to the escape of serum into the surrounding tissues The persistence of this edema, in his opinion, interfered with the nutrition of the blood vessels and led to a progression of the arterial changes, and also, as a result of increased permeability of the capillaries and veins, to hemorrhages and white patches in the retina In more recent years, Bailhart has stated the same thought in a different way when he said that local hypertension in the retina interferes with the nutrition of the arterioles and leads to sclerosis

It is of interest that the pathogenesis of the "albuminuric" type of retinitis is still not susceptible of direct experimental proof The typical retinitis has not been reproduced as yet in any experimental hypertension or nephritis so far as we have been able to determine Personally we have not observed any lesions in the retina of dogs in which marked elevations of blood urea were induced by obstructing the ureters

In 1908, Shiba injected diluted tincture of iodine into both kidneys of rabbits Within two to eight days, edema of the inner layers of the retina developed in six of nine rabbits Detachment of the retina was found in two, apparently due to subretinal exudate arising from the choroid No vascular changes were found Shiba concluded that the cause of the retinal changes lay in the altered quality of the blood, which produced an insufficiency of the vessel walls resulting in edema The lesions he described could not be considered identical with those of "albuminuric retinitis" in man

In 1909, zur Nedden immunized dogs against the renal substance of rabbits. He then injected the serum of these immunized dogs intravenously into rabbits. Within a few hours, white patches appeared in the inner layers of the retina but the typical "albuminuric retinitis" did not develop.

In their recent article on experimental hypertension in dogs, Wood and Cash did not mention lesions in the retina. In 1936 Collins (49) stated that in his dogs in which elevation of blood pressure was produced by constriction of the renal arteries, pathologic changes were not noted in the blood vessels of the retinas on histologic examination. In their original article, published in 1934, Goldblatt and his co-workers (89) did not mention any lesions of the retina in their dogs with persistent elevation of blood pressure resulting from renal ischemia.

More recently Keyes, in association with Goldblatt (139), studied the eyes of dogs and monkeys in which permanent hypertension had been produced by varying degrees of constriction of both main renal arteries. In cases in which the constriction was of moderate degree, the hypertension persisted for several years without a reduction of renal function. In cases of this type in dogs, Keyes observed increased tortuosity of the retinal arteries, progressive periarterial sheathing, hemorrhages and, occasionally, small areas of edema in the retina. These changes appeared usually after the hypertension had been present for a year or more, and such changes had some tendency to regress. Histologically, the eyes of these animals showed, in addition to some scars in the retina and choroid, thickening of the media of the retinal arteries alone or together with hyalinization of the intima and perivascular cellular infiltration. The walls of the choroidal arteries showed mainly thickening of the media. In cases of this type in monkeys, narrowing of the retinal arterioles was observed ophthalmoscopically, associated with small hemorrhages in the retina and small areas of retinal edema. These disappeared later and apparent progressive sclerosis of the retinal arterioles developed. Histologically the retinal arteries showed moderate medial thickening, and the choroidal arteries widespread and advanced disease of the intima and media.

Dogs were observed in which severe constriction of the main renal arteries was followed by hypertension associated with a rapid decrease

in renal function. In these animals, retinal and subretinal edema occurred, with edema of the disks, detachment of the retina, and hemorrhages into the aqueous and vitreous chambers. Histologic examination revealed degeneration of the arteries and arterioles throughout the eye and areas of lymphocytic cellular infiltration.

Hypertension without renal insufficiency in dogs and monkeys was considered by Keyes to correspond to benign hypertension in man. The changes found in the eyes of monkeys with this type of hypertension seemed to resemble those seen in the eyes of human subjects with acute vasospastic hypertension, or perhaps with acute nephritis. The changes found in the eyes of dogs seemed rather to be of the inflammatory type, somewhat resembling those found by Hanssen and Knack in cases of trench nephritis. Cases with a rapidly developing renal insufficiency were classified by Keyes as representing malignant hypertension. Neither the clinical course of the disease nor the ocular changes seemed to be comparable to those seen in malignant hypertension in man.

PHYSIOLOGIC MECHANISMS FOR THE MAINTENANCE OF BLOOD PRESSURE

"Normal blood pressure" of the human being is difficult to define in terms of millimeters of mercury. The blood pressures which are considered within the normal limits of health vary somewhat with the age and sex of the individual. The blood pressure of a given individual varies under conditions of exercise, emotion and the like, but, in health, these variations occur only within rather narrow limits. Wetherby made a statistical study of blood pressures of 2,282 men and 3,258 women and reached the conclusion that it is futile to attempt to draw a definite line between a normal blood pressure and an early hypertension or hypotension on the basis of single readings of blood pressure. Clinically, blood pressures which are consistently more than 150 mm of mercury systolic, or 90 mm diastolic are usually interpreted as indicative of pathologic hypertension regardless of the age of the patient. The lower limits of normal blood pressure have not been so well defined.

From a purely physiologic standpoint, the blood pressure of the normal, resting body is steadily maintained within comparatively narrow limits, mainly through the tonic and inhibitory influence

which the aortic and carotid sinus nerves (so-called buffer nerves) exert on the cardiac and vasomotor centers, on secretion of epinephrine and intrinsic tone of the peripheral arterioles

The blood pressure, which may be defined as the lateral pressure exerted on the walls of the vessels by the contained blood, is the product of the cardiac output and the peripheral resistance. An increase in cardiac output or an increase in peripheral resistance raises the blood pressure. A diminution of cardiac output or a decrease in peripheral resistance lowers the blood pressure. A delicate balance between these two factors must be maintained under normal conditions to prevent marked variations in blood pressure.

The cardiac output depends on the venous return flow to the heart, on the force of the heart, and on the frequency of the heart-beat. The factors concerned with cardiac output of most interest in their possible relationship to the pathologic rises of blood pressure with which this paper is chiefly concerned are the blood volume and the venous and capillary tone. The blood volume of the normal person is kept quite constant through adjustment of fluid interchange between blood plasma and tissue spaces and through regulation of the secretion of urine and sweat. The contractile and reservoir function of the spleen is also a factor in the maintenance of a normal volume of circulating blood. A normal capillary tone is very important for the preservation of a normal blood pressure since with the loss of tone and relaxation of the capillaries over a large area there is a reduction in the venous return flow to the heart and a drop in cardiac output. Fleisch has demonstrated the presence of reflex constriction and dilatation of the veins which also might alter the venous flow to the heart. The tone of the capillaries may be an inherent mechanism of the capillary walls. While a certain amount of resistance to blood flow is encountered in the capillaries, the velocity of flow is relatively low, so that the ultimate effect of increased capillary resistance in the raising of blood pressure is relatively small. The elasticity of the arteries is also a factor of some importance in the maintenance of normal blood pressure, since with the loss of elasticity of the arteries, as in old age, the systolic blood pressure rises higher with the same cardiac output. The rate of the heart is regulated by the nervous system through reflex stimulation of the inhibitory and excitatory centers. This mechanism

is intimately connected with blood pressure and peripheral vascular resistance

Of more direct interest in the present discussion than the cardiac output is the peripheral resistance which is resident chiefly in the arterioles. The resistance to blood flow in the arterioles depends on the viscosity of the blood, the velocity of the flow which is many times higher in the arterioles than in the capillaries, and on the size of the lumen or tone of the arterioles. Hess has enumerated the possible reflex mechanisms involved in peripheral vascular resistance.

The degree of contraction or tone of the arterioles is under the continuous control of the vasomotor center, which is situated in the floor of the fourth ventricle at the level of the apex of the calamus scriptorius. From this center, fibers pass down the spinal cord to all the thoracic and the upper two lumbar segments and end in the gray matter of the lateral horn in connector cells of the sympathetic system from which arise the vasoconstrictor fibers of the sympathetic nerves. It is of interest that these sympathetic nerves contain also some vasodilator fibers, which are also found in the posterior nerve roots. The presence of sympathetic vasomotor nerves has been demonstrated in practically all organs and tissues, in the splanchnic area, skin, skeletal muscles, large peripheral vessels, veins, capillaries, and pulmonary circulation. It was thought until recently that the cerebral vessels were controlled purely passively by the general arterial and venous pressure. It has been demonstrated by Forbes, Wolff, Cobb, and Talbott (75, 76, 47), however, that the vessels in the pia mater and also those penetrating the substance of the cortex are supplied by sympathetic nonmedullated vasomotor fibers. It is of interest that in the coronary vessels, which receive a rich innervation from both the vagus and the sympathetic, the sympathetic fibers are vasodilator and the vagus fibers vasoconstrictor in effect. It might be said in effect, then, that the maintenance of a normal blood pressure depends on the adjustment of the capacity of the peripheral vascular bed, which is a variable, to the volume of circulating blood, which is a constant. Local variations in vascular capacity are compensated for by the action of the vasomotor center on the arterioles in the unaffected parts.

The vasomotor center is under the control of high cerebral centers

to the extent that various emotions can influence the general blood pressure through stimulation or inhibition of this center. It is known, also, that the vasomotor center can function effectively only in the presence of an adequate oxygen and carbon dioxide tension. A decrease in the oxygen content of the blood in experimental animals stimulates the vasomotor center and may cause a considerable rise in blood pressure. Anoxemia does not cause a proportionate rise of blood pressure in man, however, probably owing to depression of the heart muscle. A lowered carbon dioxide tension inhibits the vasomotor center and causes a considerable fall in blood pressure, principally through dilatation of the vessels in the splanchnic area. It is true, also, that carbon dioxide acts directly on the arteriolar walls, a lowered carbon dioxide tension constricting the arterioles and a raised tension relaxing the arterioles. In man, therefore, the central and peripheral effects may neutralize each other to a considerable extent.

Recent interest has centered mainly in what Anrep has termed the "Proprioceptive mechanism of cardiovascular regulation", that is to say, the regulation of the vasomotor center and of the heart rate (vagus center) by means of reflex stimuli originating within the vascular system itself, mainly in the aorta and in the carotid sinus. The discovery of the vascular sensory area in the carotid sinus is credited to Hering in 1923. The discovery of the "aortic" or "depressor" nerve came much earlier, in 1866, by Cyon working in Ludwig's laboratory. However, the actual demonstration of its effect on the circulation was not accomplished until 1925.

In 1859, Marey observed that there was an inverse relation between the blood pressure and the heart rate, a rise in the arterial blood pressure causing a slowing of the heart. Marey explained his "law" as the result partly of the action of the blood pressure on the vagus center and partly of a purely peripheral action on the heart itself. The discovery of the depressor nerve led to the supposition that the blood pressure acted reflexly on the vagus center through this nerve, which thus constituted a safety valve regulating both the blood pressure and the heart rate. After fruitless investigations by many men during sixty years, Starling and Anrep (13) devised a method by which they could perfuse the head of one animal with blood from a heart lung preparation in another animal, while the rest of the first

animal received its blood supply from its own heart. Later, Anrep (13) and Segall substituted a heart-lung preparation for the heart of the first animal to maintain its systemic circulation and thus were able to alter the blood pressure in the head or in the aortic circulation entirely at will and independently. They were able to demonstrate that with the vagus nerves intact, a rise in the blood pressure in the head was followed by slowing of the heart rate and a fall of pressure by acceleration of the heart rate. This action is not entirely obliterated by section of the vagus nerves but is prevented by subsequent extirpation of the stellate ganglion so that the changes in the heart rate are based apparently on a reciprocal action of the cardio-inhibitory and cardio-accelerator fibers. It was demonstrated also that a rise in the aortic pressure produces a slowing of the heart rate which is reflex in origin since it disappears entirely after section of the vagi.

At the same time, Heymans was studying the same problem with the use of a somewhat different technic. His original results differed from those of Starling and Anrep, since he found that changes in the cerebral pressure produced no effect on the heart rate. Later, however, the studies of the two schools were harmonized. A high blood pressure in the thorax was found to increase the sensitivity of the vagus center to changes in the cephalic blood pressure. A low blood pressure in the thorax caused such a diminution of the vagus tone that it was difficult to demonstrate the central effect.

Hering demonstrated that a rise of blood pressure in the carotid sinus produced the same effects as a rise in the intra-aortic blood pressure. An increase of blood pressure within the carotid sinus, or pressure applied to the sinus externally, stimulates the vagus center and inhibits the vasomotor center. As a result of his experiments, Hering concluded that there is no true, direct, central regulating mechanism of the circulation. All the effects demonstrated in cross-circulation experiments can be attributed, in his opinion, to reflexes originating in the sinus region. Whether the importance of the carotid sinus is overestimated at present remains for the future to show. In any event, it has been demonstrated to have a profound influence in cardiovascular regulation. Denervation of the carotid sinus results in a considerable increase in blood pressure and in the heart rate. Later, both the blood pressure and the heart rate return almost to

normal, due to compensation by the aortic depressors. The carotid sinus also can compensate for section of the aortic depressors. If all four vasosensory "buffer" nerves are destroyed, a chronic change in the blood pressure and heart rate results, due to the abolition of vagus tone and the unrestrained peripheral constricting action of the vasomotor center. If section of these nerves is done in one stage, animals do not survive long. If it is done in two stages, however, the animals may survive for long periods and persistent hypertension. Introzzi (263) and degenerative lesions may develop in the heart, aorta and other vessels. According to Ferris, Capps and Weiss, no permanent change in either the blood pressure or heart rate occurred following unilateral denervation of the carotid sinuses of five human beings.

In this connection, an experiment is of interest with reference to surgery of the sympathetic nerves in essential hypertension. According to Kremer and Wright, if the splanchnic nerves are cut with the "buffer" nerves intact, in spite of extensive dilatation of the abdominal vessels, the fall of blood pressure is slight and transient, due to reflex compensatory vasoconstriction in other parts of the body. If the "buffer" nerves have been divided previously, splanchnic section produces a larger absolute and percentage fall of blood pressure with little evidence of recovery. Apparently, compensation cannot take place.

The aortic and carotid sinus nerves assist in the maintenance of blood pressure at a constant level in normal individuals at rest, since a rise of blood pressure increases their inhibitory activity and a fall in blood pressure lessens it and may also bring into action pressor fibers which are believed to arise from the aorta and carotid sinus. The rise of blood pressure during exercise is due mainly to increased cardiac output, since the dilatation of the vessels in the muscles outweighs the constriction in the splanchnic area and results in relatively lowered peripheral resistance.

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made up of two separate branches, one from the sensory fibers of the carotid sinus and one from the carotid body

In the experiments of Cannon and his co-workers (38, 39), the entire sympathetic system of cats was removed without significant lowering of the blood pressure. It must be assumed that arteriolar tone was restored through inherent properties of the vascular wall or by means of some unknown chemical agent. In man, however, after sympathectomy, vascular tone is never fully restored. The sympathectomized cats were able to live without disturbance in the quiet atmosphere of the laboratory but were not able to adjust themselves satisfactorily to normal outdoor life.

In discussing the relation of the suprarenal medulla to blood pressure, Wright said that there may be a constant secretion of epinephrine helping to maintain arteriolar tone and blood pressure at rest. Apparently, secretion of epinephrine is reflexly modified according to the level of blood pressure, a fall of blood pressure stimulates and a rise of blood pressure depresses secretion of epinephrine. The experiments of Heymann demonstrated that this reflex control of the suprarenal glands is accomplished through the aortic and carotid sinus nerves. Neither the suprarenal glands themselves, nor the bulbar centers controlling them, are acted on directly by the level of the blood pressure. According to Wright, there is no evidence that any other ductless gland plays any part in normal control of blood pressure. Duke-Elder asserted that pituitrin acts as a constant tonic constrictor of the minute vessels, decreasing their permeability.

The application of these general principles of cardiovascular regulation to the specific local problems of intra-ocular blood pressure and intra-ocular tension cannot be considered in detail, but a few general points might be mentioned here. Duke-Elder determined by manometric methods in the cat that the mean pressure in the ophthalmic artery is about 95 per cent and that in the retinal arteries about 70 per cent of the mean pressure in the aorta. By use of the dynamometer, Baillhart (19) estimated the diastolic pressure in the retinal arterioles to be about 40 per cent of the diastolic pressure in the brachial artery. The pressures as measured by this method may be lower than the actual figures, but they furnish a ready and probably fairly reliable method of determining variations from the normal

in pathologic states By the use of a micropipet, Duke-Elder estimated the pressure in the retinal veins to be about 2 mm higher than the intra-ocular pressure No accurate method of measuring capillary pressure has been devised, but Duke-Elder estimated the pressure in the arteriolar limbs of the retinal capillaries to be about 50 to 55 mm of mercury The intra-ocular pressure varies directly with the blood pressure in the capillaries and, therefore, can be influenced by the general arterial pressure only in so far as variations in systemic pressure penetrate to capillary circulation A rise in systemic blood pressure will be reflected in the eye But if this rise of blood pressure is accompanied by contraction of the ocular arterioles, as is usually the case, the total flow of blood through the eye is decreased and the capillary pressure falls As a result, no increase in intra-ocular tension occurs In the case of the elevation of systemic pressure caused by pituitrin, however, Duke-Elder asserts that the vasoconstriction is less marked in the arterioles of the eye than in those of other regions The increase in blood pressure is, therefore, transmitted to the capillary bed and the intra-ocular tension tends to follow the blood pressure passively

The eye is supplied by vasoconstrictor nerves through the cervical sympathetics No vasodilator nerves have been found in the eye Duke-Elder stated that, anatomically, the sympathetic fibers can be traced to the uveal vessels and also through the nerve of Tiedemann to the retinal vessels The constricting effect of these nerves on the uveal vessels has been proved by Langley and Anderson, and Henderson and Starling The vasomotor control of the retinal vessels through the cervical sympathetics has been questioned One of us (Wagener (239)) studied thirty-seven patients in whom the inferior cervical and first and second thoracic sympathetic ganglia were resected along with their intervening trunks He was able to demonstrate clinically an appreciable (measurable) dilatation of the retinal arterioles in 75 per cent of the eyes examined following this operation The veins were found to be dilated in 52 per cent of the eyes It was noted, however, that the retinal vessels tended to regain their original tone within a year following the operation

These observations are in agreement with those noted in the vessels of the rabbit's ear after experimental section of the cervical sympa-

thetic Claude Bernard noted that the dilatation of these vessels might persist for several weeks Goltz observed that the vessels later regained their normal tone or might even be more constricted than previous to the section He expressed the opinion that normal tone was regained through inherent nerve plexuses in the vessel walls He thought also that some of the primary dilatation might be due to the irritation of dilatator nerves present in the sympathetic trunk

MECHANISMS INVOLVED IN THE PRODUCTION OF PATHOLOGIC ELEVATION OF BLOOD PRESSURE

The physiologic mechanisms involved in the maintenance of normal blood pressure have been shown in the previous section to be complicated and not thoroughly understood The presence of an elevated blood pressure in the human subject adds an abnormal factor to the physiologic balance of the vascular system It is difficult, therefore, to obtain a clear conception of the fundamental cause of hypertension

There are two conditions accompanied by gross organic changes in the vascular system with which hypertension is associated The first is the rare condition of congenital stenosis of the thoracic aorta In these individuals the hypertension is limited to the upper portions of the body and one obvious explanation of this is that there is a relative increase in the blood volume in this region There is evidence that in these cases there is no histologic lesion in the arterioles of the upper extremities (95) Prinzmetal (199) believed that these arterioles dilate abnormally, but Pickering (192) was unable to confirm Prinzmetal's results Goldblatt (86), Rytand, Steele and Cohen suggested that there might be a renal factor, ischemia of the kidney, causing the hypertension in cases of coarctation Arteriovenous aneurysm or fistula, whether congenital or traumatic, gives rise to hypertension Closure of the abnormal pathway causes a momentary rise followed by a fall in blood pressure In this instance the rapid passage of a large volume of blood into the veins increases the work of the heart, which undergoes hypertrophy, and eventually hypertension develops This latter is thought to be due to increased cardiac output and increased blood volume, both of which conditions have been demonstrated in individual cases

In any discussion of the abnormal physiologic processes which may

give rise to hypertension, four obvious factors must be considered, namely, (1) increased cardiac output, (2) increased viscosity, (3) increased total blood volume and (4) increased resistance in the peripheral circulation. Increased cardiac output may be responsible for the hypertension found in some cases of aortic insufficiency and in patients with arteriovenous fistula (116, 118, 189). In many cases of essential hypertension it has been found to be normal. In some cases of polycythemia vera in which both the total volume and viscosity of the circulating blood are greatly increased, the blood pressure is normal. This is an example of the remarkable adaptability of the vascular system.

Whether or not there is increased peripheral resistance in cases of hypertension has been a debatable subject for many years. Plethysmographic studies of the peripheral blood flow in these cases have been made by Pickering, Prinzmetal and Wilson, and they indicate that constriction of the peripheral arterioles occurs but that the constricting mechanism appears to be independent of the vasomotor nervous system, as anesthetization of vasomotor nerves does not release the vascular hypertonicity. There can be little doubt that the peripheral circulation plays an important rôle in the maintenance of an abnormally high systemic blood pressure. However, actual demonstration of abnormal physiologic (200) or pathologic change has been difficult. Recent biomicroscopic methods, such as those devised by Natus, Ricker, Lombard, Sandison (206) and by Clark and his associates (44, 45), permit direct examination of these small blood vessels in the living animal. Ricker (205) demonstrated that excessive local stimulation led to constriction of the arterioles in the pancreas of the rabbit, and in turn that this caused dilatation of the distal portion of these arterioles with a slowing of the blood stream. Such phenomena suggest a similar mechanism to account for the proximal narrowing with distal dilatation of the small retinal arterioles seen by the ophthalmoscope in some cases of diffuse vasospastic disease. Clark and his co-workers (44, 45) have directly examined the blood vessels in the ear of the living rabbit, over periods of months, and have emphasized the enormous number of these vessels and the importance of the blood flow in the peripheral arterioles. They described two types of visible contraction of the arterioles and the

effect of certain stimuli produced elsewhere in the body these contractions were further studied by Wilson (255) Alterations in the actual amount of blood in the arterioles, veins and capillaries occur quickly from minute to minute, reminding one of Krogh's demonstration of the enormous increase in the number of active capillaries when muscle passes from rest to active contraction Clark and his associates studied the direct arteriovenous anastomoses in the ear of the rabbit in detail Similar anastomoses are present in the webbed feet of birds and in the fingers and toes of man (120, 94) Spanner has recently published an interesting anatomic study of the normal human kidney in which he demonstrated arteriovenous anastomoses in different regions The finding of histologic changes in the peripheral arterioles of certain patients with hypertension indicates that, in some cases, organic arteriolar lesions add another abnormal factor to the disease process (130, 134, 219) Further knowledge of these functional mechanisms and anatomic alterations in the peripheral vessels of experimental animals and of man undoubtedly will aid in our understanding of the abnormal processes in hypertensive patients and, in particular, the changes in the retina

The observation by Hartman and his co-workers that experimental lesions of the kidneys produced by exposure to roentgen rays gave rise to hypertension, and the recent demonstration by Goldblatt and his associates (89) that ischemia of the kidney of the dog and monkey (85) caused hypertension to develop have revived interest in the old problem of the relation of renal disease to diffuse arteriolar disease and hypertension Within the last year Drury (259) has demonstrated that experimental renal atrophy, and Page (272) that the experimental production of a thick fibrous capsule about the kidney, give rise to hypertension Goldblatt's original experiments have been confirmed by many observers (61, 65) Various experiments have been carried out by different investigators to ascertain whether the nervous system was involved in the production of the hypertension Hypertension has been shown to develop after denervation of the ischemic kidney (Goldblatt and Page), after transplantation into a second animal (Blalock and Levy, Glenn, Child and Heuer, Houssay and Fasciolo), after resection of the splanchnic nerves (Goldblatt and Page), after total removal of the sympathetic nervous system (Free-

man and Page), after destruction of a considerable portion of the spinal cord (Glenn, Child and Page) These results have led investigators to believe that this experimental hypertension is caused by a hypothetical effective substance or hormone having its origin in the kidney and set free into the general circulation Child's experiments seem to exclude the possibility that guanidine bases in the blood are responsible for the hypertension Thus the nature of such a circulative substance and its mode of action are still unknown Goldblatt has brought forward evidence that the suprarenal glands must be functioning if this type of hypertension is to occur (86) Although Page's results are confirmatory of Goldblatt's, those of Taquini and Collins and Wood seem to be to the contrary In this connection Allers and Kendall have shown that totally adrenalectomized dogs can be kept in excellent condition indefinitely, without the use of cortical hormone, if given a diet low in potassium and high in sodium salts Such animals apparently have a normal blood pressure and one would assume that hypertension would develop following renal ischemia In fact two experiments in the series, performed by Collins and Wood, lend support to this assumption Page and Sweet believed their experiments on dogs showed that hypophysectomy inhibited to some extent, the hypertension resulting from renal ischemia

The possible production of a pressor hormone in the ischemic kidney recalls the original observations of Tigerstedt and Bergman who, in 1898, demonstrated that a simple saline extract of the fresh cortex of the kidney of normal rabbits contained a pressor substance which they called "renin" Bingel and Strauss also obtained renin in 1909 In the last two years these experiments have been repeated and confirmed by several investigators (2, 103, 194), who employed extracts from the kidney of the rabbit, pig, dog and man Similar extracts of the spleen, intestine, muscle, brain, suprarenal glands and blood of normal rabbits and of the spleen, liver, lung and brain of the pig were inactive The most probable reason why this important contribution has, so to speak, remained buried in the literature for forty years is explained by a fact, emphasized by Pickering and Prinzmetal, that anesthetics may nullify the hypertensive reaction in the experimental animal The extract is protein like, nondialyzable, rendered inactive by heating over 60°C, and is insoluble in alcohol and acetone Fur-

ther chemical studies by Helmer and Page (262) indicate that renin contains arginine and pentose. The site of action appears to be in the peripheral arterioles and to be independent of the nervous system. This assumption, together with the results of studies of blood flow in cases of essential hypertension, suggests the possibility that arteriolar constriction in essential hypertension might be due to a renin-like substance in the circulating blood. Landis (147) and Harrison and his co-workers (162, 253) have differentiated the pressor effect of renin from that of tyramine. Renin, unlike tyramine, produces a vaso-pressor effect without reducing the peripheral blood flow. Williams and Grossman have obtained from the renal vein, after perfusing kidneys, both renin and an adrenaline-like substance. Naturally, one wonders whether such substances are playing an effective part in the regulation of blood pressure in the normal animal. The finding of renin in increased amounts over normal in extracts of ischemic kidneys of hypertensive animals suggests that such a substance stands in causative relation to this experimental hypertension.

These important experimental results of the last few years indicate that a close relationship exists between certain lesions in the kidney and systemic hypertension, as Fahr (69) has maintained for many years. On the other hand they lead to speculation as to why there can often be diffuse, destructive, bilateral renal lesions without hypertension, as for example in cases of bilateral congenital renal anomaly, chronic pyelonephritis, bilateral hydronephrosis and even sometimes in chronic glomerulonephritis.

Hypertension also occurs as a symptom of endocrine disease, it being a frequent concomitant of the syndromes which presumably result from hyperfunction of the thyroid and pituitary glands and from tumors of the medulla or cortex of the suprarenal gland. In hyperthyroidism, there is frequently a rise in systolic and pulse pressure which is thought to be due to the increased general metabolism. In cases of hyperfunctioning tumors of the suprarenal medulla, sometimes termed "paragangliomas" the elevation of blood pressure usually, but not always, occurs in paroxysms (146, 178). There is evidence that the sudden, marked rises in blood pressure are due to the release of epinephrine or closely allied substances from the tumor. Schultz, in 1929, demonstrated by pharmacologic methods that

extracts from such a tumor (in a case reported by Pincoffs), were rich in epinephrine. In 1936 Kendall isolated as much as 120 mg of crystalline epinephrine from half of a similar tumor removed surgically by Walters (136). A difficult question to answer in regard to these cases is why the pressor substance is liberated intermittently rather than continuously. Kepler recently reviewed some interesting cases of pituitary basophilism and cases of suprarenal cortical tumor in which hypertension was present. Cushing (54) advanced the hypothesis that, in the former disease, the hypertension might be the result of localized stimulation of the nuclei in the diencephalon by the hyperactive basophilic cells. Direct evidence of such a mechanism is lacking. The cause of the hypertension in cases of suprarenal cortical tumor is equally mysterious (264, 267). Most observers are of the opinion that it is probably not the result of an excessive secretion of the cortical ("salt and water") hormone which is so effective in the treatment of acute suprarenal insufficiency. Large doses of this hormone do not raise the blood pressure of normal subjects. It is of interest in these two groups of cases that clinical vascular changes seem to be identical with those seen in essential hypertension. In some cases of pituitary basophilism the retinal vascular changes and retinitis (Wagener and Kepler) and the renal changes (154) cannot be distinguished from those seen in so-called cases of malignant hypertension. Bradley and Pincoffs reported a very interesting relationship between Wilms' tumor of the kidney and hypertension. In one of their cases surgical removal of the tumor caused the hypertension to decrease, but with recurrence of the tumor, the hypertension reappeared.

Lead intoxication as a possible cause of hypertension has been a subject for controversy for many years. Temporary hypertension occurs in acute poisoning, particularly in cases of lead encephalopathy. Tscherkess (232, 233) perfused isolated arteries of the rabbit with solutions containing small amounts of lead and there was always a contraction of the arteries. This investigator also showed that, after a rabbit was chronically poisoned with lead, its arteries did not react normally to caffeine and chloral hydrate. It is of interest that acute renal insufficiency rarely occurred when acute lead intoxication developed in cases of cancer in which large therapeutic doses of lead

were given intravenously (21) Nye, in 1929, however, reported a series of fifteen cases in which, previously, during childhood, the patients had had neurologic signs of lead poisoning and later chronic nephritis both with and without hypertension had developed The lesion in the kidney was a diffuse vascular chronic nephritis Nye's experience would indicate that chronic lead poisoning can cause chronic nephritis with hypertension, evidence that such a condition develops among adults in modern industry, however, is meager and difficult to obtain (15)

In the toxemia of pregnancy, which has been termed "eclampsia," hypertension is a prominent feature The observations of Mylius and Wagener (240) that the retinal arterioles may show both localized and generalized spasm suggest that, whatever the etiologic factor of these spasms, they are probably general throughout the arteriolar system and are closely related to the hypertension A similar type of abnormal physiology would seem to be present in the group of cases which we have designated by the term "acute vasospastic disease with hypertension" and which we shall discuss later in detail The presence of an unknown toxic substance causing abnormal contraction of the arterioles, this increased peripheral resistance in turn causing hypertension, would seem to be a plausible explanation of the abnormal vascular phenomena in eclampsia and acute vasospastic disease We do not know what rôle the vasomotor center and sympathetic nervous system play in these cases Starling suggested that anemia of the vasomotor center due to arteriolar spasm might be the cause of the hypertension

According to Fishberg, "the concept of essential hypertension includes those cases of chronic hypertension which neither clinically nor anatomically can be demonstrated to have evolved from antecedent inflammatory disease of the kidneys or urinary obstruction" The primary causes of the pathologic physiology of essential hypertension are still unsolved riddles in spite of the great amount of work that has been done in attempting to unravel them Allbutt's original conception that it was primarily due to a dynamic rather than to an organic increase in the resistance in the peripheral arterioles still seems most plausible We know now, however, that early in the course of acute vasospastic hypertension there is constriction of the

retinal arterioles and that, eventually, pathologic changes occur in the arterioles throughout the body. The early lesion is medial hypertrophy, and in the more severe cases the more marked and uniform lesions are found. Such facts suggest a reaction to strain and that these lesions are not primary but secondary, and most probably secondary to hypertension just, as we believe, the myocardial hypertrophy and increased thickness of the media of the aorta (as pointed out by Karsner) is secondary to increased pressure within the arterial system. The experimental results of Wilson and Byrom (277) following ischemia of the kidney in rats support this viewpoint. Johnson, in 1868, explained his finding of medial hypertrophy in the smaller arteries as due to such a mechanism. Arteriosclerotic degenerative changes of both the larger and smaller arteries does not seem necessarily to be a cause of hypertension. Fahr and Davis have shown experimentally that increasing the rigidity of an artificial peripheral arterial system, without changes in the diameter, causes no increase in the work of the left ventricle. Weiss and Ellis demonstrated that there is no increase in the velocity of blood flow in patients who have arterial hypertension. Some have suggested the idea that the disease is due to abnormal development of arteriovenous fistulas. Such connections between the two systems are known to exist normally in the tips of the fingers and toes and, according to Spanner, in certain parts of the kidney, but they do not seem sufficient in number to give rise to hypertension. There is evidence that with sudden occlusion of a large artery, like the femoral for example, constriction of many other small arteries in the leg occurs (168). By analogy one might think of the possibility of spasm of the larger arterioles causing a similar reaction in the nearby smaller arterioles in essential hypertension. Starling suggested that anemia of the vasomotor center might be a causative factor. Bordley and Baker believed that they could demonstrate, in cases of hypertension, markedly narrowed arteries in the medulla in the region of the vasomotor centers. This finding has not been confirmed by Cutler. Increased intracranial pressure may cause a rise in blood pressure, but that such a mechanism is present in essential hypertension seems unlikely. Raab has shown that hypertensive patients react with a greater rise in blood pressure after inhalation of carbon dioxide than normal individuals. A greater

sensitivity to carbon dioxide, however, would not seem to be the primary cause of hypertension. Hypercholesteremia has been found in some cases, but the concentration of cholesterol in the blood of many typical patients with hypertension is normal.

Hyperepinephrinemia is a most suggestive hypothesis of the cause of hypertension. The well known pathologic observation that the walls of the suprarenal veins of hypertensive individuals are much thicker than those of normal persons gives support to such a theory. Several observers have tested the blood of patients with essential hypertension for pressor substances, including epinephrine, but no one has as yet demonstrated that such a substance is present in sufficient amount to cause hypertension. Pickering and others (191, 200) transfused 500 to 2000 cc of blood from hypertensive patients into anemic patients with normal blood pressure and no change occurred in the blood pressure of the latter. Major and Major and Stephenson have suggested the possibility of an increased concentration of certain guanidine compounds in the blood because of their known pressor action, but they have been unable to detect them with certainty in cases of essential hypertension. Volhard has stated that his co-worker Bohn has isolated a pressor substance in cases of so-called white hypertension. Other workers, however, including de Wesselow and Griffiths, Aitken and Wilson, and Page (179), have repeated Bohn's experiments but were unable to confirm his findings. It does seem strange if epinephrine is the primary cause, that when there is a large storehouse of extra epinephrine in certain tumors, such as is found in cases of paroxysmal hypertension, the patients do not usually have a continued hypertension nor does their condition present the course and findings so typical of essential hypertension. Lange (266) has suggested that the excessive vasoconstriction in essential hypertension is due to a decrease in the normally present vasodilating substance in the blood.

The fact that in Cushing's cases of pituitary basophilism hypertension was present has led several investigators to study the basophilic cells of the pituitary gland in cases of eclampsia and essential hypertension. Rasmussen concluded from his own histologic observations and from those of others on the cells of the pituitary gland obtained in cases of eclampsia and in essential hypertension that the

relationship of the basophilic cells of the hypophysis to elevated blood pressure is far from proved. It seems fair to conclude that, at present, we have no direct proof that the glands of internal secretion are directly related etiologically to essential hypertension. Cushing (53) has brought forward evidence of the presence of parasympathetic centers in the hypothalamus of man. Page (181) has described a syndrome simulating diencephalic stimulation, and the reaction to β -methyl-acetyl-choline, occurring in patients with essential hypertension. He did not suggest that the primary cause of the hypertension was irritation of sympathetic and parasympathetic centers in the diencephalon, but this syndrome is more prone to occur among young women suffering from essential hypertension. The relation of these higher brain centers to the maintenance and alteration of systemic blood pressure is little understood and is a fertile field for further investigation.

We have mentioned previously that various pressor substances have been held responsible for the production and maintenance of essential hypertension. Volhard felt that this assumption particularly applied to cases of malignant hypertension and that clinical and experimental facts pointed to the kidney as the principal or only source of such a pressor substance. The observation of Goldblatt and Wilson and Pickering that experimental ischemia of the kidneys of dogs and rabbits led to the development of hypertension and even diffuse arteriolar lesions (87, 254) supports Volhard's hypothesis. Moritz and Oldt also believed their pathologic studies in essential hypertension to have a similar implication. They demonstrated that there were always lesions in the arterioles of the kidney, although similar lesions were frequently absent in the arterioles in other tissues, and they therefore concluded that renal ischemia was the primary cause of the hypertension. Scott (275) also believes that renal ischemia is the primary etiologic factor in essential hypertension. Scott, Moritz and Oldt (167) do not suggest a clue as to the primary cause of the lesions in the renal arterioles. There are, however, many facts that are difficult to explain on the basis of renal ischemia. In a later section (page 356) we describe a case of chronic glomerulonephritis, in the initial acute phase of which hypertension developed, in the subacute stage the blood pressure was normal. A few years later the

typical findings of malignant hypertension developed. In this instance the histologic findings revealed chronic diffuse glomerulonephritis and arteriolar lesions throughout the tissues of the body. We interpret this case as one of chronic glomerulonephritis with the subsequent development of diffuse arteriolar disease. At present, the exact relationship between the two pathologic processes is unknown, and it is obvious that there is much still to learn regarding the etiology and development of the two conditions.

Sahlh described a series of cases in which the blood pressure was high although there was definite evidence of myocardial failure. He termed the condition "Hochdruckstaung." We have seen a number of such cases in which the patients have been in the terminal stages of essential hypertension, they presented all the signs of severe myocardial failure but the blood pressure remained markedly elevated up to the time of death. An explanation of this finding would be that the peripheral arterioles continued to be in a state of marked constriction.

Abnormal constriction of the smaller arteries and arterioles has been demonstrated in the retina in acute essential hypertension. In progressive cases, pathologic changes may eventually develop in the arterioles of the retina and in other tissues. In spite of these organic alterations, compensatory mechanisms permit temporary blood flow to the tissues. This attempt at repair is most probably due to the fundamental property of vascular tissue to form new vessels.

In essential hypertension, pathologists have emphasized the variability of the organic changes in the small arteries and arterioles, even in the course of the same vessel. From our limited knowledge of the actual anatomic distribution and physiologic mechanisms of the peripheral arterioles, one wonders, not that the pathologic changes are uneven, but that they are sometimes found to be uniform.

HYPERTENSION IN CASES OF PRIMARY RENAL LESIONS

The occurrence of trench nephritis during the World War offered an excellent opportunity for studying many of the initial effects of acute glomerulonephritis. The diagnosis was usually made very soon after the onset of the condition and the patient was immediately sent to the hospital. On admission, hypertension was often present and

persisted in the favorable cases for from five to ten days (Abercrombie) The blood pressure fell to normal coincidently with evidence of improvement, such as diuresis and diminishing edema (Keith and Thomson) During this period the fundus usually appeared to be normal, in a few cases there was slight edema about the disk margins and a few hemorrhages (132, 228) Unfortunately since arteriolar changes were not looked for, no accurate record was made of the condition of the arterioles These mild retinal changes are best explained as occurring secondary to the general toxemia which caused the disease picture, including fever and hypertension It is possible that in the fulminating case of acute glomerulonephritis the blood pressure may rise so rapidly that vasospastic retinitis with constriction of the arterioles develops We have been unable to find such retinal lesions described in the literature, unless the two cases described by Horniker can be considered to be of this type

It is of interest at this juncture to note that Arnott, Keller and Matthew have reported the development of temporary hypertension in experimental serum nephritis of rabbits The height and course of the hypertension are similar in many respects to those seen in clinical cases of acute glomerulonephritis They produced the renal lesion, a glomerulonephritis, according to the technic of Masugi They were convinced that this type of acute hypertension is reflex in origin since previous renal denervation prevents its occurrence The reflex origin of hypertension in acute glomerulonephritis has also the support of Pickering's (193) blood flow observations in clinical cases On the other hand, similar studies of blood flow in cases of chronic glomerulonephritis and essential hypertension indicate that the peripheral constriction is not due to vasomotor reflexes

In a certain number of cases of trench nephritis the delayed onset in general improvement and the slow disappearance of edema indicated a more severe type of renal disease than in the typical resolving type (46, 132) In a case mentioned by one of us (Keith (132)), edema and hypertension were still present at the end of three months In this case the retinal findings were of great interest On the seventeenth day of the disease the fundi were normal, on the fiftieth day a mild retinitis had developed and, by the ninetieth day, there was a diffuse retinitis including neuroretinal edema In a second and similar case

large areas of detachment of the retina developed R Foster Moore had a similar experience in five cases, seven to nine weeks after the onset In such cases there gradually developed the clinical and functional findings of chronic glomerulonephritis and the ultimate prognosis was not good

It is of interest that, in the experience of German observers of war nephritis, the mild edema of the disks and surrounding retina noted by Sundell and Nankivell and Keith and Thomson was a frequent finding Hanssen and Knack observed this lesion in only three of 130 cases, but most of their patients were seen rather late in the course of the nephritis Horniker found varying degrees of edema of the papilla and peripapillary retina in about a fourth of the 571 cases he examined He thought that this edema occurred as an initial symptom in practically all cases, since it was very transient and was observed most frequently in acute cases seen a few days after the onset of the nephritis Horniker noted extreme narrowing of the retinal arteries in two of these cases during an eclamptic uremic attack and, in his opinion, the edema was the expression of a transient retinal ischemia

Hanssen and Knack found retinal changes in eleven of 130 cases of war nephritis In two of these cases typical albuminuric neuroretinitis was present, but whether the patients were seen in the acute or chronic stage of nephritis was not stated As a result of their clinical and histologic studies they concluded that the retinitis which occurs in nephritis is a toxic inflammatory lesion

Horniker's series of 571 cases included chronic diffuse glomerulonephritis and malignant sclerosis as well as acute diffuse glomerulonephritis Sixty-seven patients (11 per cent) had hemorrhages in the retina and seventy-six (13 per cent) had "nephritic retinitis" Retinitis with edema of the disks, "albuminuric retinitis," was observed in six patients with acute diffuse glomerulonephritis In five of these patients the retinitis developed within eight days of the onset of the nephritis Definite narrowing of the retinal arteries was present in all of these cases Horniker was inclined to accept with reservations Volhard's theory of the ischemic origin of the retinitis

In our experience retinitis may develop in chronic glomerulonephritis as a result of three main factors edema, anemia and angiospasm

Some patients with both persistent moderate hypertension and generalized edema, quite similar to the subchronic cases of trench nephritis previously mentioned but of longer duration, may have edema in and under the retina without the usual characteristics of a retinitis. The subretinal edema may at times be sufficient to detach the retina measurably. This retinal lesion seems to be a part of the chronic toxemia which includes metabolic disturbances, especially of water, protein and inorganic salts. In our experience, however, these cases are rare (261).

In other cases of chronic glomerulonephritis in which elevation of blood pressure is absent or minimal but in which secondary anemia of a severe grade is present, hemorrhages and cotton wool patches may appear in the retina apparently as the result of increased permeability of the capillary walls. Such a retinitis cannot be distinguished in general from that seen in anemia from any other cause. In cases in which the blood pressure is mildly elevated, the presence of tonic narrowing of the retinal arterioles may help to distinguish the retinitis from that seen in primary anemias, in which the retinal arterioles are usually relatively dilated because of the associated low blood pressure and loss of vascular tone.

Acute angospastic retinitis may develop as a relatively terminal event in cases in which there have been no preceding changes in the retinal arterioles. In such cases, in the early stages of the retinitis, the arterioles show only generalized narrowing of varying grade. Anemia of the disks and the absence of localized spastic constrictions of the arterioles distinguish this type of retinitis from that seen in acute vasospastic disease with hypertension. This type is probably the most characteristic retinitis of chronic glomerulonephritis (fig. 3). Angospastic retinitis of the "albuminuric" type (with edema of the disks, diffuse edema of the retina, cotton wool patches, hemorrhages, macular stars and visible sclerotic changes in the arterioles) is seen in patients with chronic glomerulonephritis with complicating or associated diffuse arteriolar disease and hypertension. The retinitis is really that of diffuse arteriolar disease, and it is often difficult to tell from the ophthalmoscopic picture alone that glomerulonephritis has preceded the onset of the diffuse arteriolar disease. If the retinitis

is seen shortly after its onset, the presence of definite anemia of the disks is quite suggestive of the presence of glomerulonephritis (fig 4) The following is an illustrative case

A youth, aged seventeen years, on admission in January, 1925, complained of edema of one month's duration General anasarca was evident, together with albuminuria, cylindruria, microscopic hematuria, and a blood pressure in millimeters of mercury of 160 systolic and 110 diastolic The ocular fundi showed no abnormalities, except possibly slight tonic narrowing of the arterioles After the administration of an appropriate diet and diuretics, the patient became edema-free and his blood pressure became normal in one month In the next two years the patient was re-examined four times, including a careful ophthalmoscopic examination No changes occurred in the fundi during this period, nor did edema recur, the blood

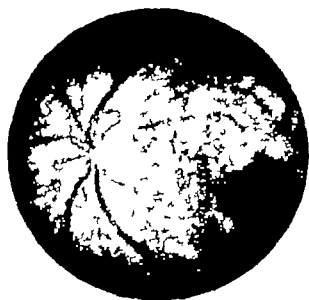


FIG 3

FIG 3 PHOTOGRAPH OF RETINA IN A CASE OF CHRONIC GLOMERULONEPHRITIS, SHOWING ACUTE ANGIOSPASTIC RETINITIS



FIG 4

FIG 4 PHOTOGRAPH OF RETINA, SHOWING RETINITIS OF DIFFUSE ARTERIOLAR DISEASE IN CHRONIC GLOMERULONEPHRITIS

pressure remained normal, but albumin and abnormal cellular elements were always found in the urine The patient continued to feel well and was at work daily until December 1, 1929, when severe headaches developed and, two weeks later, his vision began to fail He was admitted to the hospital on January 20, 1930, seemingly very ill His blood pressure was 200 systolic and 155 diastolic, the urine contained albumin (grade 2 to 3), and estimations of the blood urea and creatinine indicated severe uremia Examination of the ocular fundi revealed an edema of the disks of 4 diopters, scattered cotton-wool exudates and hemorrhages, marked constriction, and moderate sclerotic changes of the arterioles, or in other words a diffuse angiospastic retinitis of the type seen in diffuse arteriolar disease The blood urea rose to 657 mg per 100 c c before the patient died on February 1,

1930 The important pathologic findings were chronic diffuse glomerulonephritis, hypertrophy of the heart and diffuse hypertrophy of the media in the walls of the arterioles of many organs, including those of the pia of the brain, voluntary muscle, pancreas, and kidney

According to our observations, angiospastic and sclerotic lesions in the retinal arterioles, which precede the development of retinitis by any considerable period of time, are much less frequently seen in chronic glomerulonephritis than in primary diffuse arteriolar disease. When they do occur in glomerulonephritis they indicate that the nephritis has been complicated by the development of diffuse arteriolar lesions which may from then on assume the dominant rôle in the progress of the disease.

It is our impression that, in the main, retinitis is a more nearly terminal event in chronic glomerulonephritis than it is in primary diffuse arteriolar disease (261). This impression is borne out by the statistics of Fishberg and Oppenheimer, and Cannady and O'Hare. In the latter's twenty-five cases, the average length of life after the development of retinitis was six months. If one excludes the cases of two patients who lived twenty-one and twenty-three months, respectively, the average length of life of the remaining twenty-three patients was four and a half months.

The retinitis seen in a relatively large group of patients with chronic glomerulonephritis is less uniform in type than that seen in a similar group with primary diffuse arteriolar disease. However, the criteria used by O'Hare for his differentiation of "hypertensive neuroretinopathy" and "arteriosclerotic retinopathy" in cases of chronic glomerulonephritis do not seem to be very accurate, since in the majority if not all of his cases the exciting factor of the retinitis would seem to be angiospastic rather than organic lesions in the arterioles.

The record in one of our cases is unique for the length of time under observation, thirty-five years, and for the fact that a mild temporary retinitis occurred only for a period of two months when renal function was progressively decreasing.

This patient, a woman aged fifty two years and single, has sought medical advice periodically at The Mayo Clinic from January, 1902, until the present (thirty five years), her last visit being in November, 1936. In

January, 1901, at the age of sixteen years, edema of the legs had developed which was present on the patient's admission a year later. At this time the urine contained albumin in abundance. Three months later it contained much albumin and many casts. From that time until the present repeated routine urinalyses have been made and only on one occasion has albumin been absent. The blood pressure was first estimated in 1911 and was found to be 145 systolic and 115 diastolic.

In 1926, at the age of forty-two years, the patient had considerable general edema, which persisted and was considered in 1927 to be due to chronic glomerulonephritis with nephrotic features. The ocular fundi were then examined for the first time and, except for some slight reduction in the caliber of the retinal arterioles, were normal. We have records of eight subsequent ophthalmoscopic examinations in the next nine years, the last in November, 1936. In May, 1933, we had evidence of distinct impairment of renal function, the serum sulfates being 7.8 mg per 100 c c, and of moderate secondary anemia, the concentration of hemoglobin being 10.7 gm per 100 c c. Both the anemia and renal insufficiency have continued since that date. In January, 1935, the ocular fundi disclosed slight sclerosis of the retinal arterioles, anemic disks, several hemorrhages, and one cotton-wool exudate—in other words a mild retinitis probably associated with the anemia. Within two months this retinitis had disappeared and it had not recurred up to November, 1936. On this latter date the blood pressure in millimeters of mercury was 180 systolic and 115 diastolic, the blood urea was 118 mg, the blood creatinine 5.4 mg, and serum sulfates 9.8 mg per 100 c c. Even with this serious renal insufficiency the patient feels well and is quite active.

It is obvious that in some cases of chronic glomerulonephritis all three factors, edema, anemia and angiospasm, may enter into the production of the retinal picture. In certain of these cases it is sometimes difficult or impossible to state which of the factors has been mainly responsible for the onset of the retinitis.

There is a difference of opinion as to whether hypertension occurs in patients who have pyelonephritis. Most observers are agreed that hypertension may be absent for years and only develop in the later stages. Longcope, in a recent study of cases of chronic bilateral pyelonephritis, has shown that in the terminal stages, five out of fifteen of his patients had a systolic blood pressure of 200 mm of mercury or more, on the other hand, there was no demonstrable hypertension in four fatal cases. Weiss and Parker reported this year (1938) a study

of the vascular changes in chronic pyelonephritis and their relation to arterial hypertension. They believe that advancing inflammatory vascular changes and resulting ischemia initiate the hypertension, that the clinical features and histologic characteristics of vascular lesions in the kidney in chronic pyelonephritis and hypertension can be identical with those described under the syndrome of malignant hypertension. These authors estimate that chronic pyelonephritis is responsible for 15 to 20 per cent of the total number of cases of malignant hypertension of varied origin. In our series of such cases at The Mayo Clinic during the last fifteen years the percentage has been definitely lower.

There is some, although meager, experimental evidence that pyelonephritis may or may not be associated with hypertension. In 1917 one of us (Keith) and Pulford produced experimental bilateral pyelonephritis in dogs. Direct estimations of arterial blood pressure were made, after the injection of a local anesthetic, two to five months after pyelonephritis was produced in two dogs and when distinct renal insufficiency was present. The blood pressure was found to be normal. However, Prinzmetal and Friedman (198) made extracts of renal tissue which was obtained at necropsy in two cases of chronic pyelonephritis with hypertension and with these extracts produced a more marked pressor response than with control extracts in a test animal.

Butler, and Barker and Walters, have lately demonstrated an interesting relationship between hypertension and unilateral chronic pyelonephritis. In the cases of two children and one adult with hypertension the blood pressure fell and remained normal for several months after the surgical removal of the infected kidney.

At present it seems clear that pyelonephritis may or may not be accompanied by hypertension. Could the blood pressure and the hypertension in pyelonephritis follow a similar course to that seen in cases of chronic glomerulonephritis in which marked diffuse arteriolar disease later develops? (See case page 357.) Leiter has raised the question as to the relation between bilateral congenital atrophic hydronephrosis and hypertension. Then again, the exact cause of the hypertension which Schacht believed to be present in the majority of cases of long standing bilateral congenital polycystic kidneys is also not clearly understood. The development of hypertension in

these several different conditions, which are characterized by a slowly progressive renal lesion, is most probably due to more than one factor. Renal ischemia may possibly be one. However, the subject needs further observation and investigation before the exact cause or causes are known.

HEREDITY IN HYPERTENSION

Even to the casual observer it is apparent that cardiovascular disease frequently afflicts a number of persons of the same family. Reports have appeared in the literature of several families in which the incidence of vascular disease was unusually high. Thus, in 1907, Raymond recorded a family, nine members of which died of apoplexy. In 1923, Rosenbloom found arteriolar hypertension in examination of eight of ten children in one family. Both parents had died of cerebral hemorrhage. In 1925, de Nador-Nikititch found, in a study of one family, that one parent and five of eight children had hypertension. In 1923 Weitz made studies of the blood pressure of members of the families of eighty-two hypertensive patients. He stated that death from heart disease, and strokes, are much more frequent among the parents of hypertensive persons than among the parents of average people. Also, Weitz stated that deaths of this type occur at a younger age among the parents of hypertensive persons than among the parents of average people and that among the parents of younger hypertensive persons death occurs at an earlier age than among parents of older hypertensive persons. He found that parents of hypertensive persons only exceptionally reached advanced age. Weitz studied the blood pressure of ninety-three siblings of forty-two hypertensive persons. Among siblings more than fifty-five years of age, half either had hypertension or had died of it. He was not able to demonstrate exogenous causes for the hypertension in this group and he concluded that the hypertensive disease was a simple, dominant, hereditary characteristic.

In 1924, O'Hare, Walker and Vickers analyzed the family histories of 300 unselected cases of permanent hypertension. Of this group of patients, 68 per cent gave definite histories of apoplexy, heart disease, nephritis, arteriosclerosis or diabetes having afflicted one or more members of the family. The number of relatives who had vascular

disease varied from one to nine and averaged two and a half per patient. Among a control group of 436 patients who had nonvascular disease, a history of familial vascular disease was found in only 37.6 per cent.

In 1933 Ayman (17) reported studies of the blood pressure of thirty-two persons more than thirteen years of age, representing three generations of one family. He found that 100 per cent of the first generation, 80 per cent of the second, and 25 per cent of the third had elevated blood pressures. In 1934, Ayman (18) analyzed the blood pressures of 1,524 members of 277 families. He found that, in the families in which the parents had absolutely normal blood pressure, the incidence of elevated blood pressure among the children was only 3.1 per cent. In the families in which one parent had arteriolar hypertension, the incidence of elevated blood pressure among the children was 28.3 per cent. In the families in which both parents had arteriolar hypertension, the incidence of elevated blood pressure among the children was 45.5 per cent. Of seventy brothers and sisters of parents who had normal blood pressures, 37.3 per cent had elevated blood pressure. Of eighty-six brothers and sisters of parents who had arteriolar hypertension, 65.3 per cent had elevated blood pressure.

Hines and Brown (113) and their associates at the Mayo Clinic have studied the hereditary factor in essential hypertension along lines somewhat different from the purely statistical methods of the authors quoted previously. In speaking of the probable existence of a "hypertensive constitution," Volhard, although he leaned more to the assumption of an inherited inferiority of the vascular system, suggested the possibility that the wear and tear on a normal vascular system becomes accelerated through an inherited vasolability which expresses itself by abnormally strong and frequent fluctuations of blood pressure of nervous origin. O'Hare, Walker, and Vickers stated that, in the early history of hypertensive patients, symptoms often could be elicited indicating vasomotor weakness, such as frequent epistaxis, excessive menstruation, migraine, cold, sweaty and cyanotic hands, flushing, blinking, and other evidence of a high strung temperament. Such symptoms were presented by 42 per cent of their 300 hypertensive patients and by 87 per cent of 100 patients among whom these symptoms were the subject of special inquiry.

In 1932, Hines and Brown devised a standard test for measuring the maximal vasomotor response, or highest blood pressure range, of patients who had hypertension. This test consists in establishing a basal blood pressure reading by an appropriate period of rest, then placing one hand of the patient in water at 4°C and noting the blood pressure at the end of thirty seconds and at the end of sixty seconds. The hand is then removed from the water and readings are taken every two minutes until the blood pressure returns to its basal level. With this test, an individual whose blood pressure is normal shows an average increase in blood pressure of 11 mm of mercury systolic and 10 mm diastolic. The upper limit of normal increase was considered by Hines and Brown to be 22 mm of mercury. Individuals who had essential hypertension showed a much greater increase in pressures under this test. Among patients who had early or "pre-organic" hypertension, the average increase of blood pressure was 34 mm of mercury systolic and 25 mm diastolic. Among the patients who had an "organic" stage of essential hypertension, the average increase of blood pressure was 47 mm of mercury systolic and 34 mm diastolic.

In applying the foregoing "cold test" to 571 subjects, Hines and Brown (114) found a group of ninety individuals who gave normal blood pressure readings but whose response to the test was above the upper limit of normal. The average rise of blood pressure in these cases was 29 mm of mercury systolic and 24 mm diastolic. Seventy-eight of the ninety patients gave a positive family history of hypertension (86 per cent). Only 14 per cent of the group with normal reactions gave a family history of vascular disease. Within four years of the original examination, three of eight "hyperreactor normals" were known to have developed hypertension. As a result of a study of 190 members of fifteen family groups, six without and nine with definite evidence or history of hypertension, Hines and Brown expressed the opinion that the vasomotor reaction to cold follows an inherited pattern and that the excessive or hypertensive type of reaction occurs in the families in which there is a hypertensive diathesis. Eighteen per cent of 400 normal school children between the ages of five and eighteen years were found to give hypertensive reactions to the cold pressor test. They were led to believe that "the abnormality of essential hypertension is an excessive response in the blood pressure

to intrinsic and extrinsic stimulation. This abnormality is an hereditary one which appears early in life and remains during life. When the level of the blood pressure is elevated and clinical degrees of hypertension exist, the reactions then increase with increasing severity of the hypertension. This hyperreactive vasomotor mechanism may be an important factor in the production of arteriolar hypertrophy and in the subsequent development of the organic stages of the disease."

Hines and Brown thought that the mechanism of the reaction to cold was probably that of a widespread vasopressor reaction initiated through a neurogenic reflex arc. That epinephrine was not the cause was proved by the fact that the reaction occurred in adrenalectomized dogs and in patients who had Addison's disease. The reaction is not inhibited by a tourniquet placed around the arm to shut off the return of blood from the hand which is in the ice water.

These studies of Hines and Brown have been confirmed by Dieckmann and Michel, using essentially the same technic. Of six non-pregnant women who had essential hypertension, the average rise of blood pressure was 36 mm of mercury systolic and 36 mm diastolic, and of six afflicted with vasomotor irritability but who gave no family history of hypertension, the average rise of blood pressure was 37 mm of mercury systolic and 35 mm diastolic. Of twenty-eight non-pregnant women who gave a family history of hypertension, the average rise of blood pressure was 35 mm of mercury systolic and 34 mm diastolic, while of forty-two nonpregnant women who gave no family history of hypertension, the average rise of blood pressure was 18 mm of mercury systolic and 23 mm diastolic.

Hines and Brown found that the systolic form of hypertension seen in cases of senile arteriosclerosis and in cases of glomerulonephritis gave definitely less response to the cold pressor test than did the pre-existent and existent stages of essential hypertension. This fact is of particular interest with regard to the constriction and sclerosis seen in the retinal arterioles of certain patients who give apparently normal blood pressure readings (115). One of us (Wagener) has believed that these changes, if definite, are always associated with hypertensive disease since they must indicate a tendency to generalized arteriolar constriction and sclerosis. The cold pressor test was applied by Hines

and Brown to fifty patients of this type, ranging in age from thirty-four to sixty-five years. The mean reaction in blood pressure for the group was 38 mm of mercury systolic and 26 mm diastolic. In 70 per cent of the cases the return to the previous basal level was abnormally prolonged. Hourly readings of the blood pressure of ten of the group so studied revealed marked lability. Eighty-two per cent of the patients gave positive family histories of cardiovascular disease. In this connection, Brown (115) suggested that the abnormal vasomotor reactions of patients of this type might be due to the absence of a normal controlling factor rather than to the presence of an abnormal pressor substance.

It seems obvious, then, that certain individuals who have this inherited, abnormal vasopressor response to stimuli may have constriction and sclerosis of the arterioles for some time before they give the usual clinical signs of hypertensive disease. The fact that this early phase of the disease may be visible in the retina before it is manifested elsewhere, except by special functional tests, offers a valuable field for clinical research to the ophthalmologist who wishes to study, along with the internist and physiologist, the early phases and modes of development of vascular disease. An extensive study of the caliber of the retinal arterioles of children and adults of different ages might be of considerable value in this respect.

TOXEMIA OF PREGNANCY

Observation of patients with the toxemias of the later months of pregnancy affords an excellent opportunity for studying certain phases of hypertensive disease. Most of these toxemias are complicated by, or associated with, a rise in blood pressure. Any classification of the toxemias must take into consideration two main facts: (1) that primary glomerulonephritis or essential hypertension may exist before the onset of pregnancy and may undergo exacerbation in the course of the pregnancy with resultant toxic manifestation, and (2) that the blood pressure may rise acutely or gradually coincident with, or preliminary to, the appearance of symptoms of toxemia in a previously normal patient. The presence of pregnancy introduces special problems in the management of glomerulonephritis and essential hypertension, but otherwise, of course, the diseases are identical with those in the

nonpregnant individual. The cases in which elevation of blood pressure occurs more or less rapidly in a previously normal patient present, however, some points of especial interest.

In this latter group of cases it is questionable whether eclampsia, with its characteristic lesions in the liver and kidneys, is basically different from pre-eclamptic toxemia in which the principal objective manifestation is elevation of the blood pressure. As noted by Herrick and Tillman in 1934, in most obstetric clinics every woman with high blood pressure is classified as having nephritis. Obviously this is not true. It is equally obvious, however, that while most pre-eclampsias and eclampsias are vasospastic in type, clinically some patients with eclampsia present more evidence of renal damage than others and, in some cases, generalized edema is so striking as to justify the diagnosis of a nephrosis or of an acute nephritis with nephrotic manifestations. The similarity of these cases to certain cases of trench nephritis in the male is striking. These patients present a retinal picture which is predominantly that of subretinal edema, often sufficient in degree to detach the retina without any of the usual manifestations of retinitis. The mode of development and postpartum course in these cases are not identical with those in cases of the predominantly vasospastic type. Accordingly, if we assume the presence of a circulating toxin or pressor substance common to all cases, we must assume that this toxin has a varying affinity for different tissues in different cases. The presence of such a substance in the blood of these patients has never been conclusively demonstrated.

The fact that all elevations of blood pressure seen in the course of pregnancy are not secondary to primary nephritis is conclusively demonstrated by the studies of Corwin and Herrick and Herrick and Tillman. They stated that clinical follow up studies in cases of toxemia marked by hypertension as the dominant feature, and with albuminuria secondary and subsiding, appear to reveal the stigma of hypertensive cardiovascular disease rather than of primary nephritis. In their series of eleven cases of persistent cardiovascular-renal disease following pregnancy which came to necropsy, the pathologic diagnosis was primary glomerulonephritis in four cases and primary cardiovascular disease with arteriolar sclerosis in seven. Herrick and Tillman suggested that patients in the vascular group have a tendency

toward hypertension before the onset of pregnancy. It is of interest to note in this connection, however, that the results of Hines and Brown's "cold test" were not uniformly positive in this group of cases.

Until comparatively recent years the findings of "albuminuric retinitis" in a pregnant patient has been universally considered to be diagnostic of chronic nephritis. Thus in 1915 Miller stated, "It has been my experience that albuminuric retinitis of pregnancy affords evidence strongly indicative of primary nephritis." In 1924 Cheney admitted, in agreement with Schiotz, that retinitis does occur in acute toxemias of pregnancy without evidence of a pre-existing nephritis and that a few of these patients do not show evidence of residual nephritis. Most authors, especially among the obstetricians, attempt to differentiate between "retinitis" and "albuminuric retinitis" and state that the latter always indicates chronic nephritis. Personally, we do not believe that there is any distinction between these two "types" of retinitis except the time element, since most patients who show primarily a few cotton-wool patches and hemorrhages will later develop the characteristic picture of "albuminuric retinitis" unless the pregnancy is terminated spontaneously or otherwise. In our opinion, also, in the case of the pregnant woman as in that of the non-pregnant woman, the albuminuric type of retinitis is more often the result of diffuse arteriolar disease than it is of primary glomerulonephritis. The following cases illustrate these two points.

A woman, aged thirty-six, was admitted to the hospital in September, 1920, in the sixth month of her first pregnancy. On a previous visit to the clinic in 1919 her blood pressure had been recorded as 142 systolic and 100 diastolic. The blood pressure had shown a tendency to rise rather early in the course of the pregnancy and, in the fifth month, was 160 systolic and 120 diastolic. At the time of her admission to the hospital the patient's blood pressure was 224 systolic and 120 diastolic, and during her stay it ranged between 192 and 220 systolic and 112 and 140 diastolic. The urine contained albumin, grade 3 to 4. The concentration of urea in the blood was 44 mg per 100 c c. Ophthalmoscopic examination revealed marked hypertensive changes in the retinal arteries. On the fourth day cotton-wool patches and hemorrhages appeared in the retina, and these gradually increased in number. Induction of labor was advised but was refused. By the end of two weeks the classical picture of "albuminuric retinitis"

had developed. On October 6, nineteen days after admission, labor was induced and a non viable fetus was delivered. From this time on the retinitis gradually subsided. Six months after delivery, in April, 1921, the blood pressure was 170 systolic and 116 diastolic, the urine contained albumin, grade 2, and the concentration of urea in the blood was 54 mg per 100 c.c. Ophthalmoscopic examination revealed rather marked retinal arteriosclerosis with residual postretinitic scarring. Three and a half years later, in November, 1924, the blood pressure was 230 systolic and 130 diastolic, the urine contained albumin, grade 2, the concentration of urea in the blood was 35 mg per 100 c.c., the concentrating and diluting powers of the kidneys were fair, and the retinitis had not recurred. The hypertension was considered to be of the essential type. One and a half years later, in February, 1926, the patient had a cerebral vascular accident, with a resultant right hemiplegia from which she made a very good recovery. About one year later, in April, 1927, the patient had a recurrence of the retinitis and showed definite evidences of renal and myocardial insufficiency. The concentration of urea in the blood was 68 mg per 100 c.c. and an electrocardiogram showed inverted T waves in leads I, II, and III, which indicated left ventricular strain. The blood pressure at this time was 230 systolic and 140 diastolic. One year later, in May, 1928, the patient died at home, apparently as the result of the hypertensive disease. Necropsy was not obtained.

A woman, aged forty-one, was admitted to the hospital in April, 1920, in the seventh month of her eighth pregnancy. Her blood pressure was 250 systolic and 160 diastolic. Her urine contained albumin, grade 3, and many casts. The concentration of urea was 40 mg per 100 c.c. of blood. Extensive diffuse retinitis of the albuminuric type was present in each eye, with edema of the disks and star figures in the macular regions. At that time the diagnosis was chronic glomerulonephritis with nephritic retinitis. The patient was delivered five days after her admission. Sixteen months after the termination of pregnancy the systolic blood pressure was 180 and the diastolic 130. Ophthalmoscopic examination revealed sclerosis, grade 3, of the retinal arteries, with residual scars in the retina and choroid and some pallor of the disks but no recent retinitis. With the exception of the occurrence at times of small hemorrhages in the retina, the retinal lesions did not change essentially during the remaining period of observation. In November, 1924, four and a half years after the original toxemia, the patient returned to the clinic because of a left hemiplegia and left homonymous hemianopia, apparently the result of a cerebral hemorrhage or thrombosis. The systolic blood pressure at this time was 170 and the diastolic 110.

Urinalysis gave negative results except for indicating the presence of albumin, grade 1. The concentration of urea was 10 mg per 100 c c of blood. The patient made a very excellent recovery from both the hemiplegia and hemianopia, but three and a half years later, in May 1928, she died as the result of a second cerebral vascular accident. Necropsy revealed hypertrophy of the heart (it weighed 548 gm as compared with the normal of 300 gm for a person of corresponding height and weight), multiple old and fresh cerebral hemorrhages, and generalized arteriosclerosis,

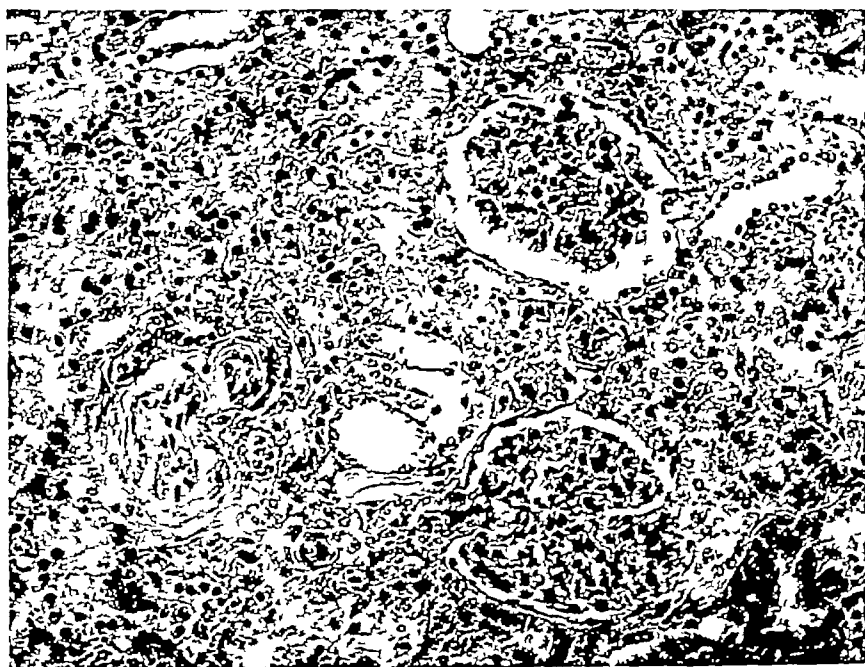


FIG 5 KIDNEY AT NECROPSY IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 2, SHOWING ARTERIOLOSCLEROSIS WHICH WAS RESIDUAL OF TOXEMIA OF PREGNANCY

The kidney otherwise was normal (hematoxylin and eosin $\times 190$)

grade 2, with arteriosclerotic changes, grade 1, in the kidneys. The glomeruli were well preserved and the rest of the renal tissues were essentially normal. The pathologic diagnosis was essential hypertension with fresh cerebral hemorrhage (fig 5).

Until comparatively recent years, essentially no studies were made of the retinal arteries in cases of toxemia of pregnancy prior to the onset of retinitis, and no adequate study of the vessels had been made even in the presence of retinitis. This probably was largely because

ophthalmologists were rarely called to see these patients until they complained of disturbance of vision, at which time retinitis was usually well established and considered as definite evidence of the presence of chronic nephritis. In 1918, Volhard suggested that generalized arterial spasm, not renally conditioned, was responsible for the hypertension, convulsions and renal symptoms in eclampsia. The careful studies of Mylius on the retinal arteries, published in 1928, furnished the first demonstration that arterial spasms did occur in toxemia of pregnancy, that they antedated definitely the appearance of retinitis, and that they might disappear without leaving any visible organic change in the vessel walls. About the same time we at The Mayo Clinic were observing these transitory changes in the retinal arteries of patients with the toxemia of pregnancy and noting that they were



FIG 6 PHOTOGRAPH OF RETINA SHOWING NARROWING OF ARTERIOLES GRADE 2, AND SCLEROSIS GRADE 2+ A RESIDUAL TO RETINITIS OF THE TOXEMIA OF PREGNANCY

not always associated with retinitis and were not necessarily followed by retinitis if the pregnancy was terminated shortly after their first appearance. If one assumes with Friedenwald that the development of anoxemia in the retina is demonstrated by the appearance of retinitis and that the retinal tissue lysis resulting from the anoxemia secondarily cause organic changes in the vessel walls (fig 6), it seems logical to assume that organic changes will not develop in the arteries if the pregnancy is terminated at the first suggestion of retinal anoxemia. This assumption is supported by the results. Thus of nineteen patients with acute toxemia of pregnancy who had not had hypertension previous to pregnancy and who showed during the toxemia arteriolar spasms but no retinitis, only one had persistent

hypertension following pregnancy whereas of fourteen patients of the same type who showed arteriolar spasms with retinitis, eleven had persistent hypertension and the three who had no residual hypertension showed only a few cotton-wool patches and hemorrhages in the retina, which rapidly disappeared With the observation of a larger series of cases it has become obvious that permanent organic changes do take place at times in the arteriolar walls after persistent spasm without the development of ophthalmoscopically visible retinitis If it were possible to determine definitely the earliest signs of these organic changes, more patients might be spared the onset of generalized arteriolosclerosis and persistent hypertension A valuable field for further investigation is open here to ophthalmologists for the determination of signs or tests to distinguish purely spastic from definitely organic lesions of the arterioles

It is of interest that in the toxemias of pregnancy the presence or absence of spasms in the retinal arterioles cannot be definitely correlated with the height of the blood pressure Often, the condition of the retinal arterioles seems to be a more reliable guide to the severity of the toxemia than is a single determination of the blood pressure This is not necessarily true, however, if twenty-four hour studies of the blood pressure are considered rather than single readings Ophthalmoscopic examination is only one of the aids to the estimation of the severity of any type of vascular disease However, the field of toxemia of pregnancy is one in which close co-operation between ophthalmologist and internist or obstetrician can be of great value both to the patient and to our knowledge of the basic processes involved in the development of hypertension The studies of Masters and Hallum in the United States have essentially confirmed the findings of Mylius The accompanying photographs illustrate the localized spasms of the retinal arterioles observed by Mylius and Hallum in toxemias of pregnancy (figs 7, 8 and 9)

Dieckmann and Michel studied the response to the "cold test" of Hines and Brown (114) of a group of pregnant women with toxemia They found that in thirty-four cases of pre-eclamptic toxemia the average increase in blood pressure during the test was 26 mm of mercury systolic and 23 diastolic In five cases of eclampsia the average increase was 26 systolic and 16 diastolic The increase in

blood pressure was not as great as in a group of thirteen normal, pregnant women with a family history of hypertension among whom they had found an average rise of blood pressure of 35 mm systolic and 28 diastolic. However, in a group of thirty-three pregnant women

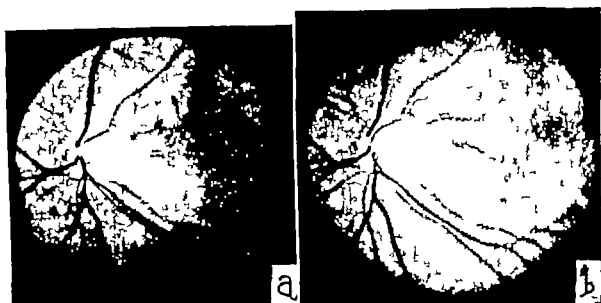


FIG 7 PHOTOGRAPH OF RETINA

Case of Dr K. Mylius *a*, spasm of arterioles in toxemia of pregnancy, *b* after recovery

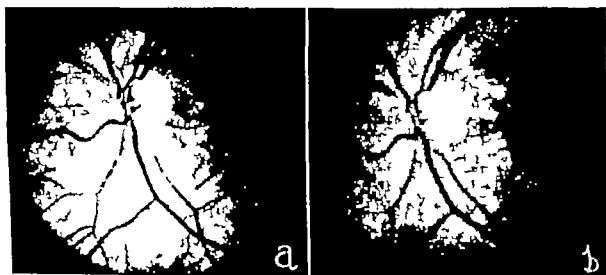


FIG 8 PHOTOGRAPH OF RETINA

Case of Dr K. Mylius *a* spasm of arterioles in toxemia of pregnancy *b* after recovery

with chronic nephritis, including some with primary hypertension, chronic glomerulonephritis, and recurrent toxemia of pregnancy, the average increase in blood pressure was 51 systolic and 37 diastolic. These figures remained essentially the same in this group after the termination of pregnancy.

Dieckmann and Michel suggested as possible explanations for the relatively low response of patients with pre-eclampsia and eclampsia (1) that in these cases vascular spasm may already be at its height, and (2) that there may be in these diseases lowered sensitivity to pain. Whatever the explanation, it seems logical to assume that not all patients with pre-eclamptic toxemia or eclampsia have a preliminary hypertensive background and that some of them, at least, should have normal vascular systems after the termination of pregnancy if the toxemia is adequately controlled.



FIG 9

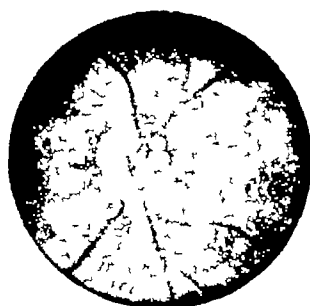


FIG 10

FIG 9 PHOTOGRAPH OF RETINA (CASE OF DRS HALLUM AND CLAY), SHOWING SPASM OF ARTERIOLES IN TOXEMIA OF PREGNANCY

FIG 10 PHOTOGRAPH OF RETINA IN A CASE OF VASOSPASTIC DISEASE WITH HYPERTENSION, SHOWING ACUTE ANGIOSPASTIC RETINITIS

ACUTE VASOSPASTIC DISEASE WITH HYPERTENSION

Since Mylius and Wagener observed and described visible vasospastic changes in the retinal arterioles in cases of eclampsia, several observers have reported cases, in which the patients were males or nonpregnant females, that simulated many of the features of eclampsia. The characteristic findings are acute onset, with a quick rise in blood pressure and rapidly developing retinitis (fig 10). These cases differ from those of acute glomerulonephritis in that the evidence of renal damage is minimal or absent. The following case, reported by Haben and Wagener, is noteworthy.

The patient was a man, aged forty-two years. He had been examined at The Mayo Clinic at the ages of thirty-four and forty-one years respectively and had been found to be healthy. The only definite illnesses he had had were several attacks of tonsillitis and quinsy, he had had mild

symptoms of peptic ulcer Three weeks before his admission, the illness for which he presented himself had begun with sudden onset of severe head ache, some nausea, blurring of vision and increase in blood pressure to 220 mm of mercury systolic and 135 diastolic On physical examination the blood pressure was 220 systolic and 130 diastolic, the heart was not enlarged, the pulse rate was 90, there was no edema (fig 11) Ophthalmoscopic examination revealed bilateral, acute, diffuse retinitis with edema of the optic disk, diffuse edema of the retina involving the macular region, cotton-wool patches and hemorrhagic areas in the retina. The retinal arterioles

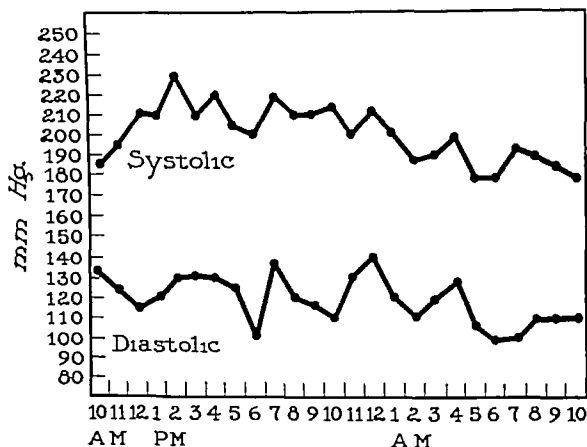


FIG 11 ACUTE VASOSPASTIC DISEASE WITH HYPERTENSION

The blood pressure of this patient was determined each hour for twenty four hours

were generally narrowed but there was no evident localized spasm or sclerosis A few days later, however, definite localized spasms were visible On routine analysis the urine showed a trace of albumin and a few erythrocytes, the number of erythrocytes per cubic millimeter of blood was normal The concentration of hemoglobin and urea in the blood, the value for serum sulfate, and the results of the urea clearance test were also normal Decrease in the sulfate clearance and failure of the specific gravity to rise above 1 020 were the only distinct abnormalities in renal function Tonsillectomy was done On the patient's dismissal, three weeks after admission, the retinitis was receding and the blood pressure was 130 systolic and 80 dia

stolic The patient was seen subsequently on five occasions in the next year He felt well throughout Within six months the retinitis had disappeared One year after the onset, the blood pressure was 165 systolic and 110 diastolic, there was only mild narrowing and sclerosis (fig 12) of the retinal arterioles, the urine was protein-free and renal function was normal Naturally, we do not know what the ultimate course in this case will be During the first year, however, there has been little to suggest a diagnosis of glomerulonephritis

It is of interest to note that Mahomed, in 1879, described similar cases without evidence of nephritis The patient's condition, after the initial severe episode, seems best described as a mild form of diffuse arteriolar disease which the authors would consider as belong-

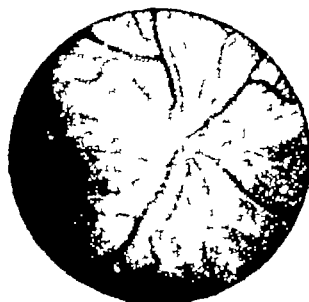


FIG 12 PHOTOGRAPH OF RETINA IN A CASE OF ACUTE VASOSPASTIC DISEASE WITH HYPERTENSION, SHOWING NARROWING OF ARTERIOLES, GRADE 1, AND SCLEROSIS, GRADE 1, A RESIDUAL OF ACUTE ANGIOSPASTIC RETINITIS

ing to group 1 The characteristics of cases of group 1 and of other groups are given in the section on essential hypertension

The course of the disease in the foregoing case has been very favorable so far The residual damage to the retinal arterioles is minimal and the persistent hypertension of a low grade The end result, however, in these cases of acute vasospastic disorder is not always so satisfactory, for just as in the toxemias of pregnancy, the persisting hypertension may be progressive and severe Such a case (133) will now be outlined

The patient was a woman, who after having been under observation for many years for other illnesses, became afflicted within a few months by a severe form of arteriolar disease with hypertension The patient first came to The Mayo Clinic in 1914 when she was eleven years of age and thus has

been under our observation for eighteen years. When she was aged seventeen years, cervical adenitis developed, and two years later the diagnosis of tuberculous nodes was made histologically following surgical operation. At the age of twenty-one years she had her first baby, without any untoward events during pregnancy. Three years later the vision in her left eye became poor. Her second pregnancy, at twenty six years, was normal, there was no albuminuria or hypertension throughout. The ocular fundi were normal except for the presence of healed tuberculous chorioretinitis in the left macular region. The next year, 1930, routine urinalysis gave

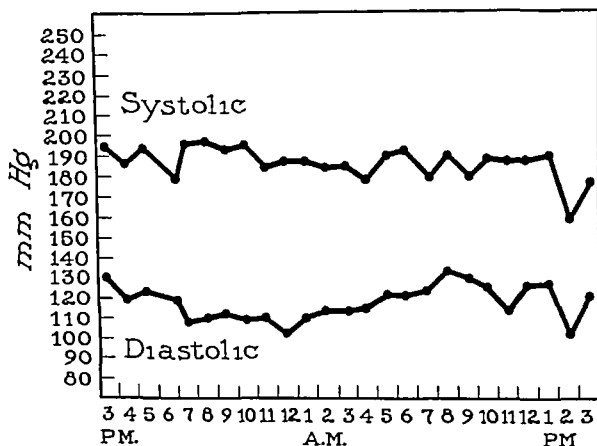


FIG. 13 ACUTE VASOSPASTIC DISEASE WITH HYPERTENSION

The blood pressure of this patient was determined each hour for twenty four hours

results which were negative, as they had been on previous visits. In March, 1932, the blood pressure was 110 systolic and 70 diastolic. Previous to that date the records of blood pressure were also within the limits of normal. In August, 1932, the patient came in for refraction because of headaches. No lesion was found in the fundus except the old central chorioiditis of the left eye.

In November, 1932, because of increasing severity of the headaches the patient was thoroughly examined again. The systolic blood pressure was 220 and the diastolic, 140 (fig. 13). The arterioles of the ocular fundi were markedly attenuated but there was no retinitis. On routine urinalysis albumin, grade 3, was discovered but casts or erythrocytes were not

found The value for blood urea and serum sulfate was normal although the urea clearance was reduced to 25 c c Two weeks later the patient was brought into the hospital in a stuporous condition She was apparently totally blind, but two hours later she perceived moving objects and had left homonymous hemianopia Ophthalmoscopic examination revealed marked constriction of the retinal arterioles, with considerable spastic irregularity Hemorrhages and cotton-wool exudates were present in the right retina The next day the woman could read a newspaper and the visual fields were normal There was no actual paralysis During the next three weeks, the typical "albuminuric" retinitis of so-called malignant hypertension (group 4 in our classification) developed, with edema of the optic disks, numerous cotton-wool patches and hemorrhagic areas, and in the right eye there was a partial macular star, the arterioles were markedly

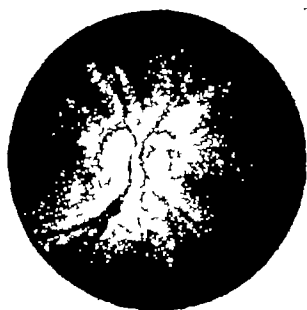


FIG 14 PHOTOGRAPH OF RETINA IN A CASE OF ACUTE VASOSPASTIC DISEASE WITH HYPERTENSION

The arterioles are narrowed, grade 2 to 3, and sclerosed, grade 3, and there is perivascular thickening This was a residual of acute angiospastic retinitis

constricted Examination of arterioles of a small portion of the pectoralis major muscle, removed for histologic study, disclosed a decreased ratio of lumen to wall, 1/4, and a moderate increase in the intimal and medial nuclei Within a month of admission the patient slowly began to improve and the retinitis to subside Eight months later there were residual signs of the retinitis but no active lesions Twenty months after the onset of the retinitis there were still slight residual signs of retinitis The arterioles of the retina were still markedly narrowed and were definitely sclerosed, grade 3, as can be seen in figure 14

This condition had not changed up to the time of the last examination of the patient in August, 1936 (a period of three years) The patient's general condition continued to be good until right hemiplegia developed on May 25, 1935 She again gave evidence of remarkable recuperative powers and in spite of some weakness of the right arm and leg she has been able

to do part time work since In August, 1936, the patient was well nourished, her weight was normal The retina still appeared as in figure 14 The blood pressure was 205 systolic and 135 diastolic On routine urinalysis a moderate amount of albumin was found but there were no erythrocytes or casts The concentration of blood urea and of serum sulfate was normal although the clearance of both was moderately reduced The concentration of hemoglobin in the blood was 12.8 gm per cent, a figure only slightly below normal

Following the acute vasospastic phase in this case the course was rather favorable for two years In spite of the development of right hemiplegia a year ago the patient is still able to do a portion of her housework It is noteworthy that in this case diffuse arterial disease was present and accurate observations were made for four years, during this period, distinct secondary anemia or serious renal insufficiency did not develop Such findings are not usual in cases of progressive, diffuse, glomerulonephritis

Koenigsberger and Bannick and Beaver (141, 142), in 1932 and 1933, reported a case in which hypertension and symptoms of diffuse vasospastic arteriolar disease developed a short time after an attack of septic sore throat

The patient was a man, aged twenty nine years, who on admission had a blood pressure of 180 systolic and 140 diastolic, there was no retinitis and routine examination of the blood and urine and certain tests of renal function gave negative results. While the patient was under observation, three different types of pain developed (1) severe and cramp-like pain in the abdomen, (2) severe headache and (3) substernal attacks which were coronary in type These symptoms gradually lessened, and in five weeks the patient considered that he had recovered At this time a specimen for biopsy was taken from the pectoralis major muscle and histologic findings were rather meager, except that there was some increase in the nuclei in both intima and media The patient remained symptom free for the next year However, approximately eighteen months after the onset, the patient showed the typical findings of severe, diffuse arteriolar disease with hypertension The retinitis was that of group 4, with edema of both optic disks, and renal studies revealed albuminuria and some reduction in renal function At this time a second biopsy revealed decided changes in the walls of the arterioles, some of the arterioles were completely closed by hypertrophy of intima and media The subsequent course of the disease

was rapid. The patient died within two years of the initial symptoms. Necropsy revealed the typical pathologic findings of group 4, described by Kernohan and his associates (135, 138) in 1928 and 1929 and by Cain in 1934.

This case, in our opinion, is an example of acute vasospastic hypertensive disease which ran a short course, terminating within two years. During the terminal phase the clinical and pathologic features were those of so-called malignant hypertension. As in the previously outlined case, there were many features that one does not associate with acute, subacute, or chronic glomerulonephritis.

We have so far described three cases that presented features of diffuse arteriolar spasm. It is of interest to recall that ophthalmologists for many years have observed and described the occurrence of local arteriolar spasm in the retina. Elschnig and Wagenmann have recorded transient blindness associated with occulsive spastic constriction of the retinal arterioles. Coincident with the quick return of vision the spasticity of the retinal arterioles disappeared. Similar cases have been followed by Wagener and Gipner. The following case is an outline of the sequence of events in one of their cases.

A physician's wife, aged forty-five years, gave the history that respectively seventeen years and twelve years previously she had had two miscarriages at the sixth month. Between these miscarriages she had a normal pregnancy. All three pregnancies were accompanied by albuminuria but the blood pressure was not ascertained. For twelve years she had short periods of partial or complete blindness and for four years white or dead fingers. On examination there was slight anemia, the systolic blood pressure was 160 and the diastolic, 100. On routine urinalysis albumin, grade 2, was found but there were no abnormal elements in the sediment. The excretion of phenolsulfonphthalein was 45 per cent in two hours. While the retina was being examined with the ophthalmoscope, an occulsive spasm of a branch of the left inferior temporal artery was observed as an attack of blindness occurred in the upper nasal field. The spasm and blindness persisted for one to two minutes and then disappeared. Four, and again eight, years later the patient was examined and was found to be in good health. She reported that the attacks of blindness were less frequent and that her general health was improved.

The probable sequence of events in this case was the development of eclampsia with a residual tendency to hypertension, arteriolar

spasm in the retina, and recurrent arterial spasm giving rise to the white fingers

The significant fact which should be stressed is that occlusive arterial or arteriolar spasm can occur in the retina and tissues generally for a short period and leave no demonstrable injury of tissue. If, however, the spasm persists for more than a few minutes an anemic infarct results

ESSENTIAL HYPERTENSION

Whenever the etiology of a disease is obscure, classification or grouping of cases is a difficult problem. Bright struggled with the various clinical syndromes associated with pathologic kidneys one hundred years ago, and even today the differentiation of types of renal disease is far from satisfactory. So-called essential hypertension is in a similar category. The most widely known classification is Volhard's "red" and "pale" hypertension which we have discussed in previous sections. We must admit the merits of Volhard's basic conception of those two conditions, and the stimulus it has given to further study. On the other hand, our own studies have convinced us that such a grouping is not entirely satisfactory.

We began our joint studies of essential hypertension in 1920. By 1924 we were able to report a small series of cases, which seemed to form a clinical and pathologic entity. Further observation in similar cases, including one of a child (reported elsewhere in detail by Amberg) permitted us to collect in all eighty-one cases and those were reported in detail in 1928. The condition was termed "the syndrome of malignant hypertension." Many of the cases differed from the bösartig hypertension of Volhard and the malignant nephrosclerosis of Fahr in that our diagnosis frequently was made before there was serious impairment of retinal, cerebral, cardiac and renal functions. The retinal findings varied in degree but certain distinct changes always were present. The course of the disease was rapidly progressive and its seriousness is evident from the fact that within a year of the time the diagnosis was made, 78 per cent of the eighty-one patients had died.

With further study it became obvious that there were many cases of essential hypertension which did not belong in this group of rapidly progressive cases, nor could they be termed cases of "benign" or

"simple" hyperpiesia Gradually a group could be identified in which the presence of mild vasospastic retinitis was an important diagnostic feature The course was less rapid and remission of symptoms sometimes occurred We have identified another group, the salient features of which are more marked hypertension and more distinct narrowing and sclerosis of the retinal arterioles than that encountered in the benign cases and yet there is no demonstrable break in retinal, cardiac or renal functions

To avoid confusing descriptive terms the groups have been given numbers We have termed the usual benign cases as belonging to group 1, those with more marked hypertension, but few untoward symptoms and no retinitis as of group 2, those with mild vasospastic retinitis as of group 3 and those with the so-called malignant hypertension syndrome as of group 4

Kernohan (135), in examination of pathologic material obtained at necropsy in our cases belonging to group 4, found that changes in the arterioles were often widespread throughout the body Similar findings since have been reported by Murphy and Grill (269), Scott, Seecof and Hill, Pilcher and Schwab, Moritz and Oldt, and Ellis ^{2 3} For this reason it seemed that study of the arterioles in tissue obtained for biopsy would give information concerning the peripheral arterioles in life in cases of the four groups Skeletal muscle was chosen because it represented a large portion of the body's weight and was less subject to local disease which might involve the blood vessels The pectoralis major muscle was selected because of its accessibility This study began in 1927, and between that date and 1932 the arterioles of muscle from 138 patients who had hypertensive disease were examined Control observations revealed that the normal ratio of lumen to wall is 2.0, the variation is 1.7 to 2.7

This histologic study disclosed that in some cases the arterioles appeared to be normal while, in many other cases, the walls of the arterioles were thickened, the ratio of the diameter of the lumen to the

²For details of the renal pathologic findings in malignant nephrosclerosis see (1) Fahr, (2) Klemperer and Otani, (3) Shapiro, and (4) Schurmann and MacMahon and (5) Cain (6) Russell, Dorothy S (274)

³For details of diffuse pathology see (1) Keith, Odel, Morlock Rosenberg, and Kernohan, (2) Morlock, (3) Odel, (4) Rosenberg, (5) Davison and Brill

thickness of the wall was definitely decreased. This was most marked in cases of group 4. In many cases this change was uniform for all the arterioles seen. In some, it was confined to the smallest arterioles and in others there were marked variations and localized changes only. Other changes which we have termed qualitative have been noted in the muscle arterioles in many cases. These consist of increased prominence and tortuosity of the arterioles and an increase in the number and size of medial and intimal nuclei. We have observed occasionally organized thrombi, extensive intimal proliferation, complete occlusion of the lumen by simple hypertrophy of the media and perivascular collections of lymphocytes and fibroblasts. Pilcher and Schwab (196) have actually observed medial necrosis in the arterioles of voluntary muscle in a case of malignant hypertension, although we have never seen it in our material. Thus medial necrosis has been found in the arterioles of voluntary muscle as well as in those of the kidney and other organs in malignant hypertension. None of these changes has been found in the histologic sections of muscles of individuals with normal blood pressure. Similar findings to ours have been noted by Scott, Seecof, and Hill (figs 15, 16, 17, 18, 19 and 20). *Changes similar to those found in the arterioles of striated muscle can be demonstrated in the arterioles of the retina (figs 21, 22, 23, 24, 25 and 26a, and b)*

In addition to this histologic study of the arterioles of muscle in 138 cases belonging to the four groups, a follow-up record was kept in every case up to January, 1937, or nine years from the time when the first, and five years from the time when the last, patient was examined. In addition we continued to follow up the eighty-one cases belonging to group 4 (reported in 1928). Thus there are follow up records on 219 cases of all groups (table 1). In considering the characteristics of the individual groups we shall stress certain clinical observations and evidence of comparative arteriolar changes as seen in the retina by means of the ophthalmoscope and as seen in the muscle when it is examined microscopically.

In the present attempt to group cases of essential hypertension clinically, we realize that not all cases fall into one of the four groups mentioned. There are many patients who have this condition who have, in addition to arteriolar dysfunction, diffuse arteriosclerosis,

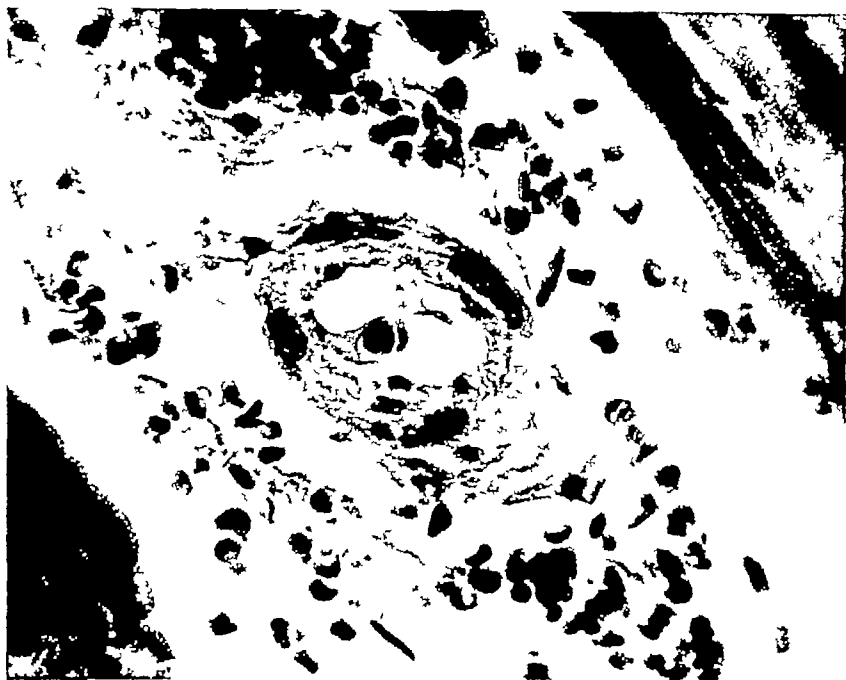


FIG 15 BIOPSY SPECIMEN FROM PECTORALIS MAJOR MUSCLE, SHOWING NORMAL ARTERIOLE

The ratio of lumen to wall is 2.0 (hematoxylin and eosin $\times 550$)

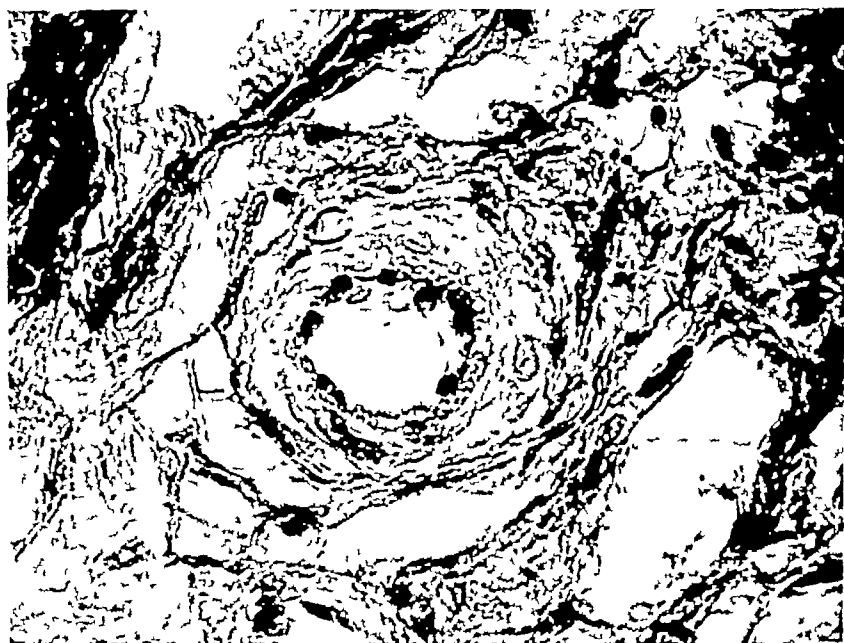


FIG 16 BIOPSY SPECIMEN FROM PECTORALIS MAJOR MUSCLE IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 3, SHOWING HYPERPLASIA OF INTIMA

The ratio of lumen to wall is 1.5 (hematoxylin and eosin $\times 700$)



FIG 17 BIOPSY SPECIMEN FROM PECTORALIS MAJOR MUSCLE IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4 SHOWING HYPERTROPHY OF MEDIA

Ratio of lumen to wall is 1.0 (hematoxylin and eosin $\times 475$)

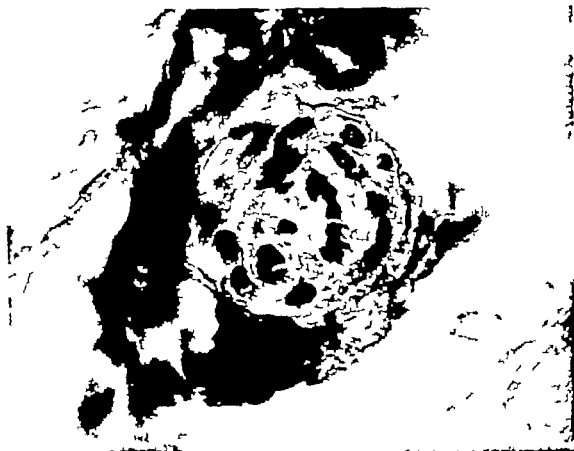


FIG 18 BIOPSY SPECIMEN FROM PECTORALIS MAJOR MUSCLE IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4 SHOWING MARKED HYPERPLASIA OF INTIMA AND MEDIA

(Hematoxylin and eosin $\times 675$)



FIG 19 BIOPSY SPECIMEN FROM PECTORALIS MAJOR MUSCLE IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4, SHOWING ORGANIZED THROMBOSIS IN LUMEN (Hematoxylin and eosin $\times 675$)

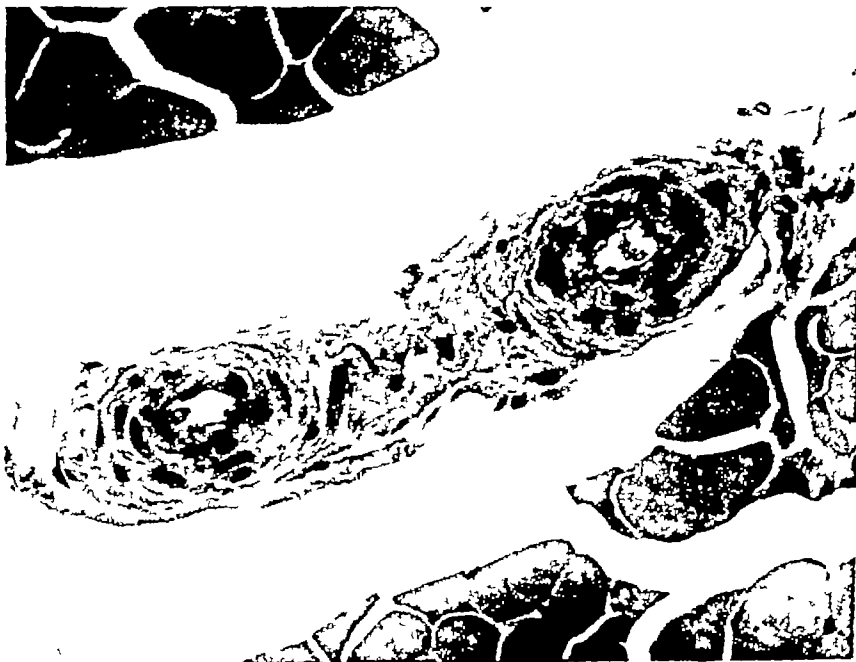


FIG 20 BIOPSY SPECIMEN FROM SKELETAL MUSCLE (CASE OF DR R W SCOTT) IN DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION

Two arterioles show thickening of media and narrowing of lumen (hematoxylin and eosin $\times 370$)



FIG 21 RETINA AT NECROPSY IN A CASE OF CHRONIC GLOMERULONEPHRITIS SHOWING
NORMAL ARTERIOLE

Ratio of lumen to wall is 3.5 (hematoxylin and eosin $\times 500$)



FIG 22 RETINA AT NECROPSY IN A CASE OF DIFFUSE ARTERIOLAR DISEASE
WITH HYPERTENSION OF GROUP 4 SHOWING MEDIAL HYPERTROPHY OF
ARTERIOLE

Lumen to wall ratio is 2.6 (hematoxylin and eosin $\times 500$)

more especially of the aorta and of the coronary and cerebral arteries. Atherosclerosis of these arteries may be the determining factor as to the course and prognosis. With more knowledge relative to the occurrence of atherosclerosis in such vital internal arteries, and with the aid of more accurate diagnostic methods, these cases might be grouped in a much more satisfactory manner than is possible at present.

*Diffuse arteriolar disease with hypertension, group 1*⁴ Many of the cases described by Allbutt (9), Janeway and others (276) as cases of



FIG 23 RETINA AT NECROPSY IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4, SHOWING MEDIAL HYPERTROPHY OF ARTERIOLE

Lumen to wall ratio is 1.8 (hematoxylin and eosin $\times 500$)

essential hypertension belong in this group. They recognized that such a condition is compatible with continued good health, indeed some of their patients were observed for twenty years. Luckily, at present this group of cases constitutes the great majority of those of hypertension. A study of blood pressure for twenty-four hours in one of the cases seen at The Mayo Clinic demonstrated the decided

⁴We believe the important dynamic and histologic changes are in the arterioles. There are, however, always coexisting changes of varying degree in the arteries.

effect of rest on the hypertension (fig 27) The retinal changes in this condition are usually minimal and consist of mild narrowing or mild sclerosis of the arterioles The following case was typical of the group



FIG 24 RETINA AT NECROPSY IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4 SHOWING MEDIAL HYPERTROPHY OF ARTERIOLE

Lumen to wall ratio is 1.3 (hematoxylin and eosin $\times 500$)

The patient, a man aged thirty eight years, was first seen in 1918 At that visit the ocular fundi were normal Neither at this time nor on his second visit in 1924 was hypertension present In 1930 the man was fifty years of age at which time he had hypertension, the systolic pressure was 210 and the diastolic, 130 He had headaches and he had noticed increased irritability for two years The retinal arterioles were generally narrowed grade 1 In July, 1932, the blood pressure was taken over a period of

twenty-four hours His cardiac and renal functions were good The retinal arterioles were sclerosed, grade 1 (fig 28) The patient usually feels well and carries on his regular work as a schoolmaster

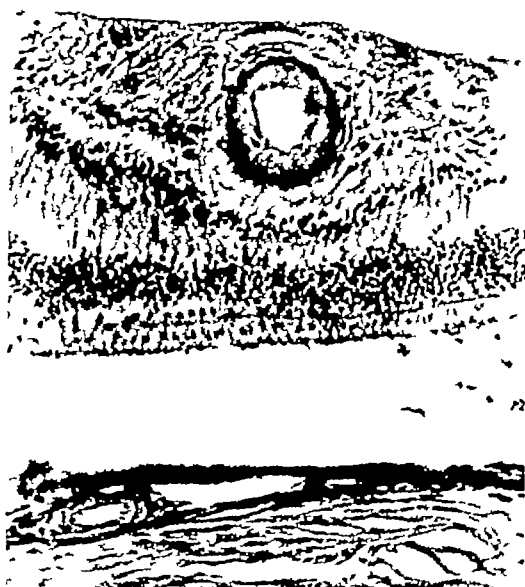


FIG 25 RETINA AT NECROPSY (CASE OF DR J S FRIEDENWALD), SHOWING HYALINE DEGENERATION AND THICKENING OF MEDIA OF A RETINAL ARTERIOLE

TABLE 1

Age at time of first examination

HYPERTENSION, GROUP	NUMBER OF PATIENTS			AGE	
	Male	Female	Total	Range	Mean
				<i>years</i>	<i>years</i>
1	7	3	10	30-65	55
2	14	12	26	21-59	41
3	22	15	37	22-57	42
4	99	47	146*	8-64	40
Total	142	77	219		

* Biopsy of muscle carried out in 65 cases

Muscle was taken for biopsy in ten cases The ages of the patients in these cases were thirty to sixty-five (mean fifty-five) years Microscopic examination of the arterioles gave a mean ratio of lumen to wall of 1.7, with a variation of 1.3 to 1.8, and disclosed definite histologic

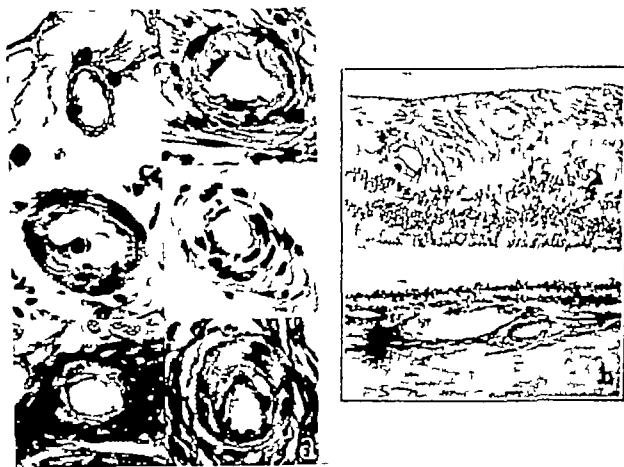


FIG 26a COMPARISON OF HISTOLOGIC APPEARANCE OF ARTERIOLES OF NORMAL INDIVIDUALS (LEFT) WITH THOSE OF PATIENTS WITH DIFFUSE ARTERIOLAR DISEASE AND HYPERTENSION OF GROUP 4 (RIGHT)

Hematoxylin and eosin upper Retinal arteriole $\times 500$ middle Muscle arteriole (biopsy) $\times 550$ and 475 lower Renal arteriole $\times 650$ and 350 b Retina at necropsy (case of Dr J S Friedenwald) showing complete occlusion of the lumen of a retinal arteriole by thickening and hyaline degeneration of the media.

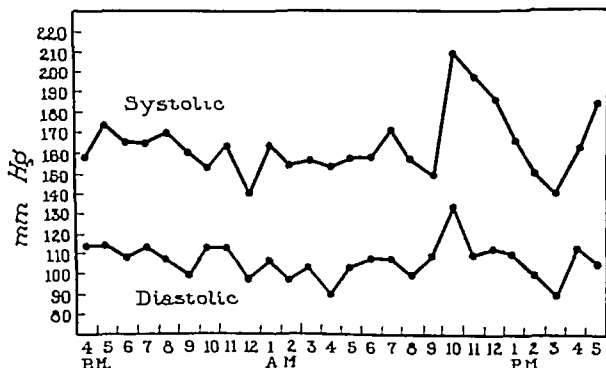


FIG 27 DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP I
The blood pressure was determined each hour for twenty four hours

lesions in one case Six patients are alive, 86 to 105 months after biopsy Four patients are dead, two died of coronary disease, one of typhoid fever, and one of pneumonia



FIG 28 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 1

The retinal arterioles are narrowed, grade 1, and sclerosed, grade 1

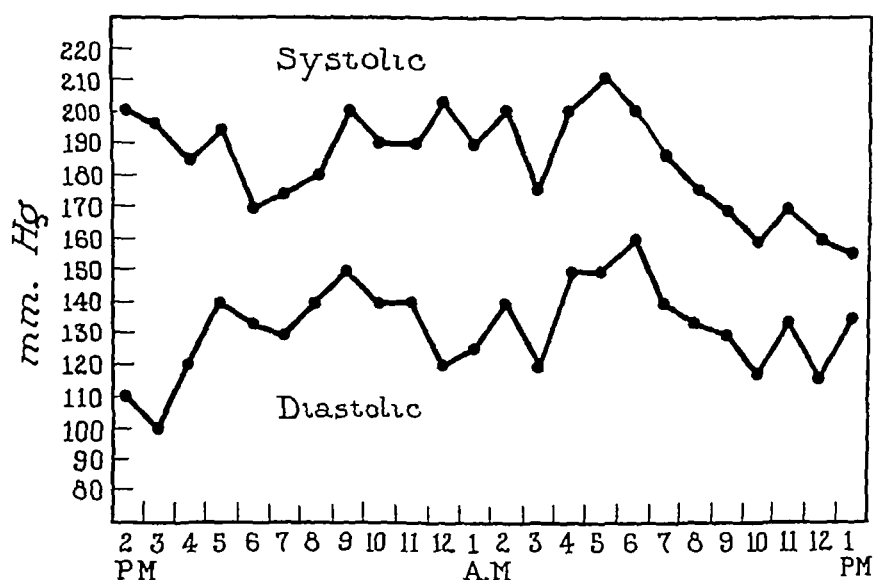


FIG 29 DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 2

The blood pressure was determined each hour for twenty-four hours

Diffuse arteriolar disease with hypertension, group 2 Patients of this group have a continuously higher blood pressure (fig 29) and more distinct changes in their retinal arterioles (figs 30 and 31) and muscle arterioles than those of the previous group, but they still are in good general health The following is such a case

In 1928 a woman, aged twenty three years, was known to have had hypertension and headaches for six months. The retinal arterioles were generally narrowed, grade 2, and were mildly sclerotic. The arterioles of the muscles, on histologic examination, were definitely altered. Cardiac and renal functions were good. The patient's health remained satisfactory for four years. Then more serious symptoms began to develop and in 1934 the patient presented the terminal picture of so-called malignant hypertension. In the ocular fundi there were diffuse retinitis with edema of the disks of *three diopters* and *macular stars*. The woman died in August, 1934. Necropsy was not permitted.



FIG 30

FIG 30 PHOTOGRAPH OF RETINA (CASE OF DR. A. J. BEDELL) SHOWING SCLEROSIS, GRADE 2, OF RETINAL ARTERIOLES



FIG 31

FIG 31 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 2

The retinal arterioles are narrowed, grade 1 to 2 and sclerotic grade 3

One's impression of the patients in this group is that the disease is more progressive and has produced more severe and diffuse arteriolar changes than in the cases described under group 1. Histologic studies of the muscle arterioles of twenty-six patients, aged twenty-one to fifty-nine (mean forty-one) years disclosed more uniform and more marked narrowing than was evident in group 1. The mean ratio of lumen to wall was 1.3, with a variation of 0.8 to 1.9, and definite histologic lesions were observed in eleven cases, in three of which thrombosis or occlusion of arterioles was seen. Follow up data revealed that nine patients were alive 74 to 107 months later, and seventeen were dead. It is of interest that one of the living patients was first examined at the clinic in 1920 and at that time the systolic blood pressure was 210 and the diastolic, 120, so it appears that patients belonging to this group may live comfortably for many years.

Diffuse arteriolar disease with hypertension, group 3 Group 3 includes cases in which there is marked hypertension and readily demonstrable, diffuse arterial changes with evidence of functional insufficiency of certain organs. Abnormal features are most easily demonstrated in the retina, brain and kidneys. An important criterion is the presence of angiospastic retinitis, together with definite sclerotic changes in the arterioles but no edema of the disks. Cardiac and renal functions may be adequate but usually give evidence of early impairment. A brief outline of such a case follows.

A woman, in 1929, was aged thirty-five years and at that time was known to have had hypertension for six months. Examination of the retinal arterioles revealed sclerosis, grade 2, spastic in type. Three years later

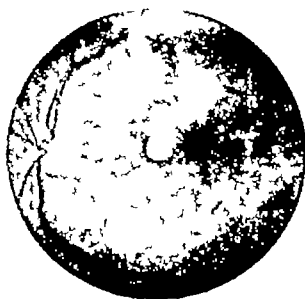


FIG 32 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 3
Arteriolosclerotic phase

headache and pain in the legs had developed. Within these three years the condition had changed from that of group 2 to that of group 3. Moderately extensive retinitis of angiospastic type was present but no edema of the disk (fig 32). The systolic blood pressure rose to 260 and the diastolic to 160 (fig 33). There was albumin, grade 3, in the urine, but adequate renal function, the concentration of blood urea was 32 mg per cent. There was no serious cardiac dysfunction.

It is of great interest that even in cases of group 3 there may be remission in the activity of the pathologic process. The patient feels better and stronger and headache or vertigo may be absent. There is evidence in the retina of previously active retinitis and many small arterioles may become obliterated. In one such case a number of small arterioles of the retina had undergone thrombosis and on biopsy

the same process was seen to have taken place in some arterioles of the skeletal muscle. One naturally wonders if cessation of arteriolar spasm could be responsible for the remission.

The muscle arterioles were examined histologically in thirty seven cases in which the age limits were twenty-two to fifty seven (mean forty two) years. The ratio of lumen to wall was 1.0 to 2.0, mean 1.3, and definite cellular lesions were present in ten cases, with thrombosis or occlusion in eight. The prognosis was serious, for in seventy-nine to ninety months after examination, thirty four patients were dead.

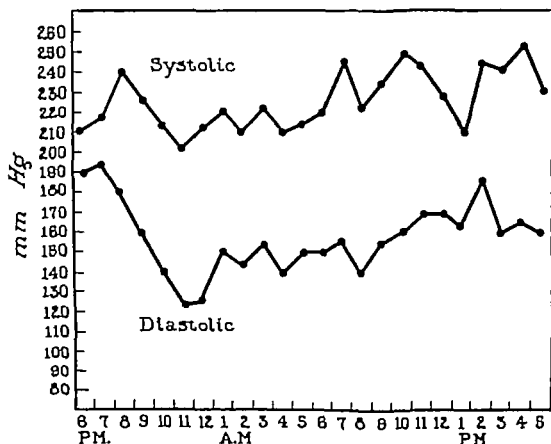


FIG. 33. DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 3. The blood pressure was determined each hour for twenty four hours.

and only three living. One of the latter, however, seven years after the biopsy of muscle was made, is well and the blood pressure has been as low as 130 systolic and 90 diastolic.

Diffuse arteriolar disease with hypertension, group 4. All observers are agreed that the patients of this group are in a very serious condition. This fact is further emphasized by our follow up study in 146 cases. In these cases, approximately 80 per cent of the patients died within one year. The characteristic symptoms are nervousness, asthenia, visual disturbances, dyspnea on exertion and nocturia.

There may also be obvious neurologic lesions. The objective findings are persistently elevated blood pressure (fig 34), diffuseness of arterial and arteriolar thickening throughout the body, minimal changes in parenchyma of kidney (fig 35) and retinal changes. The important retinal alterations are the marked spastic and organic narrowing of the arterioles, with diffuse retinitis and edema of the disks. The following case is an example of a rapidly progressive condition.

A man, aged thirty-seven years, when first examined in March, 1932, was up and about. He had had hypertension for two years and headaches

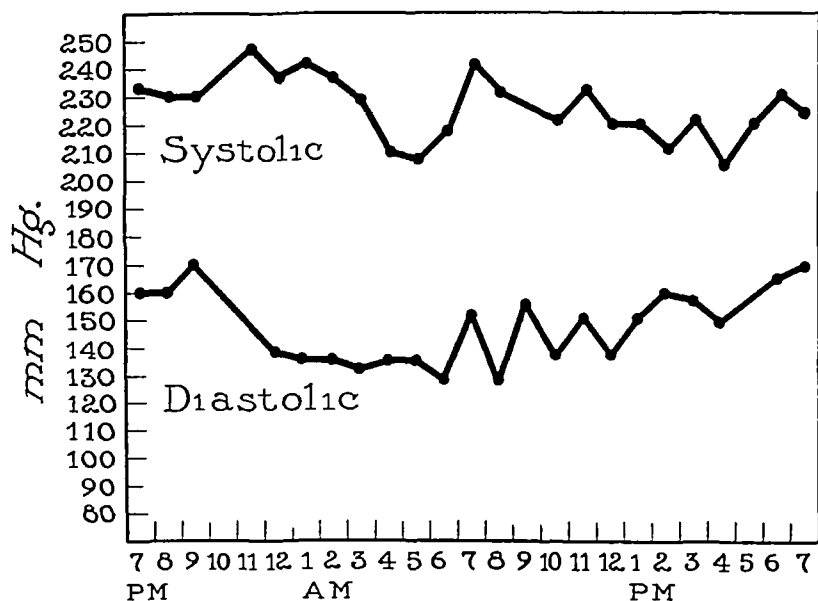


FIG 34 DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4
The blood pressure was determined each hour for twenty-four hours

for eighteen months. Gross hematuria, which had appeared ten days before, caused him to come to the clinic. Slight failure of vision had been noticeable for one year. The appearance of the ocular fundus was typical of cases of group 4. The retinal arterioles gave evidence of sclerosis, grade 3, with diffuse retinitis of angiospastic type and measurable edema of the disks (fig 36). Diffuse arterial disease was evident. Marked albuminuria and gross hematuria were present. The concentration of blood urea was 38 mg per cent. One month later, diffuse pain in many muscles appeared and then came blurring of vision of the left eye. About two months after the patient's first visit, the ocular fundi had not altered except that fresh edema had appeared in the region of the left macula. The patient died

soon afterward from cerebral, cardiac and renal insufficiency. The value for blood urea rose to 232 mg per cent. The concomitant sudden failure of these three vital organs is further evidence of the diffuseness of the arteriolar lesions.

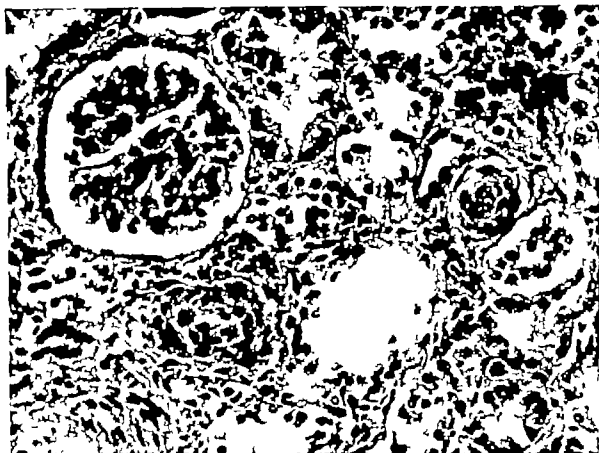


FIG 35 KIDNEY AT NECROPSY IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4 AND ARTERIOSCLEROSIS. The glomeruli are normal (Hematoxylin and eosin $\times 275$)

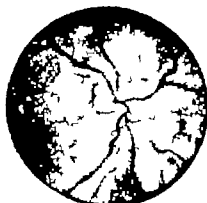


FIG 36 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4

Not in all cases of group 4 is the course so rapid. Some patients even have periods with subsidence of the retinitis and with clinical symptoms which suggest remission. Such cases belonging to group 3

were considered previously Here again in group 4 spasm of the arterioles may determine whether the condition is progressive Such subsidence of severe retinitis was noted by Liebreich, who gave the first detailed description of the ophthalmoscopic findings in albuminuric retinitis in 1859 Fishberg and Oppenheimer, in 1930, reported in a case of malignant hypertension the healing of severe retinitis with no recurrence over a period of four and a half years We reported a similar case in 1929 and since that date we have seen four additional cases We have observed a few cases of group 4 in which the course

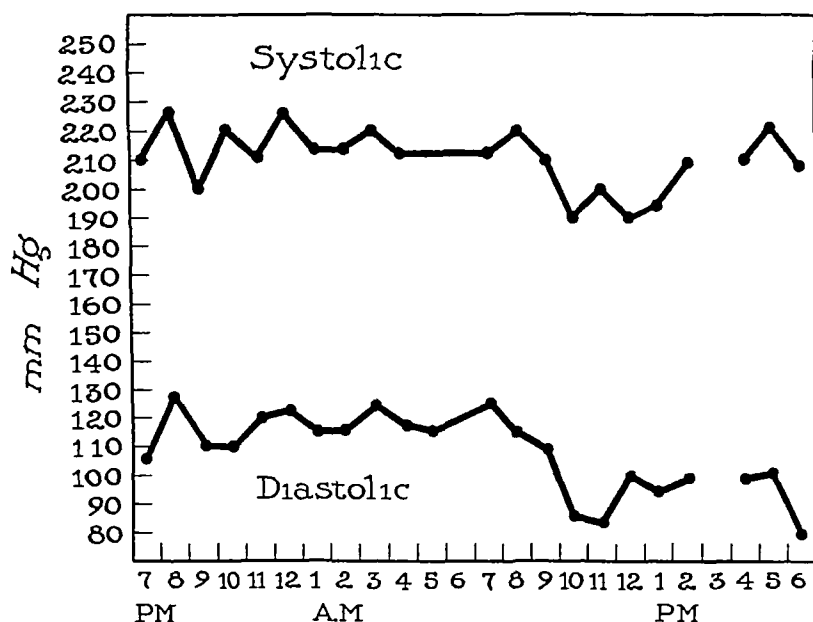


FIG 37 DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4

There were distinct vasospastic findings and a rapid course The blood pressure was determined each hour for twenty-four hours

was very rapid and in which there were various symptoms such as sudden severe headaches, hematuria and muscle pains, accompanied by a persistent high blood pressure (fig 37), marked narrowing of the retinal arterioles and absence of distinct histologic changes in the muscle arterioles A progressive angiospastic mechanism seems to offer the best explanation Evidence is also accumulating that even when there is marked pathologic change in the arterioles, compensatory mechanisms, at present obscure, may still permit periods of improved tissue metabolism

The arterioles of muscle obtained by biopsy were subjected to histologic examination in a series of sixty-five cases of group 4. The age limits of the patients were eight to fifty eight (mean thirty eight) years. The ratio of lumen to wall in the arterioles was 0.9 to 1.8 (mean 1.2), there were cellular lesions in thirty-one cases and in eighteen of these there was thrombosis or occlusion of the lumen. The prognosis was serious, only one patient lived as long as forty months. Seventy nine per cent were dead within a year. However, a single case of the original group of eighty-one cases of group 4 was alive, eleven years after her first visit.

Clinical differentiation of the four groups of cases is usually not difficult. Patients of groups 1 and 2 necessarily must have good retinal, cerebral, cardiac and renal function, whether the hypertension be labile, or high, with a tendency to fixation. In cases of group 3 there is evidence of dysfunction of one or of several of the organs belonging to the arterial system, while in group 4 these functional disturbances become more definite and final failure may occur because of a simultaneous serious interference in the blood supply to the retina, brain, heart and kidneys. A given case may be markedly progressive and pass from group 1 to group 4 in a short period. On the other hand, there are cases in which there is little progression over a period of many years, the majority of these belong to group 1 but a moderate number to group 2 and a few to group 3. Because the arterioles throughout the organs of the body seem to be the chief point of attack and can be readily visualized only in the retina, the findings obtained by the ophthalmoscope are very important.

Examination of the ocular fundi is of considerable aid in determining the group in which an individual patient with hypertension should be placed. Theoretically, patients who have only purely organic changes in the arterioles of the retina should belong to group 1 or group 2, while patients who show any definite evidence of angiospasm (fig. 38) should be placed in group 3 or group 4. Practically, it is often impossible to say definitely of certain individuals, whether irregular narrowings of the retinal arterioles are actively angiospastic or whether they are the result of previous angiospasm now quiescent. So that, in the main, it seems better to place such patients tentatively in group 2 until the lapse of sufficient time to determine whether or

not retinitis will develop For, from the ophthalmoscopic standpoint, the presence of an angiospastic type of retinitis is the only definite criterion for the inclusion of a patient in group 3 or group 4

Patients who have only mild narrowing (increased tonus) or sclerosis of the retinal arterioles usually will fall into group 1 Patients usually are placed in group 2 if they have moderate to marked sclerosis of the retinal arterioles, whether of chronic type, characterized especially by exaggeration of the arterial reflex and arteriovenous compression, or of postangiospastic type, characterized especially by generalized and localized irregular narrowing of the arterioles Thrombosis of the retinal veins is considered to arise either on the basis of organic

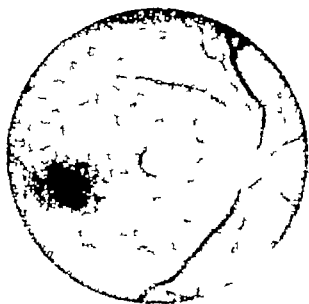


FIG 38

FIG 38 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION (CASE OF DR A J BEDELL), SHOWING SPASM OF RETINAL ARTERIOLE

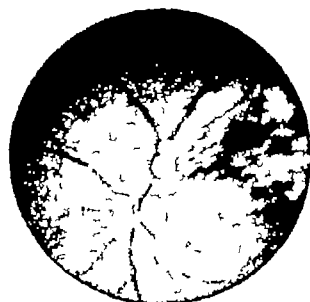


FIG 39

FIG 39 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 2

There was recent thrombosis in a superior temporal vein

changes alone or as the result of an infectious process (phlebitis) superimposed on a mild organic lesion Patients with retinal venous thrombosis usually belong in group 2 (fig 39), although the other clinical and laboratory findings at times may justify their classification with hypertension of group 3 Cases of retinitis of arteriosclerosis (Foster-Moore type) usually can be placed in group 2 unless the retinitis can be shown definitely to be the residuum of a previously angiospastic type of retinitis The principal differentiation in many instances between these two types of retinitis lies in the absence, or the presence, of cotton-wool patches, and it must be remembered that such patches may have been present previously and may recur The definite diagnosis of retinitis of arteriosclerosis seems to us to be

justified at a single examination only when evidences are demonstrable of localized organic lesions in the arterioles or veins of a sufficient grade and in the proper distribution to account for the retinal lesions

Patients with retinitis of angiospastic type, characterized especially by edema, cotton wool patches and hemorrhages in the retina superimposed on a combination of sclerotic and spastic lesions in the arterioles, fall into hypertension group 3 or group 4. Patients who have cotton-wool patches and hemorrhagic areas in the retina, but whose optic disks are not edematous, usually belong to group 3 (fig 40). The most characteristic feature of the disease in cases of hypertension of group 4 is measurable edema of the optic disks, which usually occurs, of course, in association with the other features of



FIG 40

FIG 40 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 3



FIG 41

FIG 41 PHOTOGRAPH OF RETINA IN A CASE OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION OF GROUP 4

widespread angiospastic retinitis. In some cases, however, other evidences of retinitis are strikingly few (fig 41). The diagnosis of malignant hypertension (group 4) should not be made, however, on the basis of ophthalmoscopic examination alone, in the absence of other clinical and laboratory evidence, unless definite signs are present of sclerosis of the arterioles which antedated the onset of the retinitis. This reservation is made because of the occasional occurrence of acute angiospastic retinitis, with edema of the disks, in cases of acute vasospastic hypertension.

Cases of acute angiospastic retinitis which occur in association with acute vasospastic disease with hypertension are of particular interest, both to the ophthalmologist and to the internist (243). As in retinitis

in association with toxemia of pregnancy, the ophthalmoscopic picture may vary from that of localized areas of edema of the retina, with cotton-wool patches and hemorrhages, to that of the classical "albuminuric" type of retinitis, with edema of the disks and diffuse edema of the retina. Also, as in toxemia of pregnancy, the retinitis may completely disappear under favorable circumstances, leaving as residuals varying grades of sclerosis of the retinal arterioles, depending on the severity and persistence of the underlying angiospasm (fig 42). The characteristic diagnostic feature in such cases in the early stages of the retinitis lies in the presence of marked evidences of angiospasm, generalized and localized irregular narrowing of the arterioles, and absence of organic changes in the vessel walls, such as



FIG 42 PHOTOGRAPH OF RETINA IN A CASE OF VASOSPASTIC DISEASE WITH HYPERTENSION, SHOWING THROMBOSED TERMINAL ARTERIOLES, A RESIDUAL OF ACUTE ANGIOSPASTIC RETINITIS

visible thickening of the wall, exaggerated reflexes and arteriovenous compression. In the later phases of the retinitis, when organic changes are developing in the walls of the arterioles, differentiation from the ordinary types of retinitis seen in association with hypertension of group 3 or group 4 may be difficult or impossible. In cases in which there is a favorable response to treatment, however, the retinitis, even when measurable edema of the disks has been present, can subside with surprisingly little residual, visible, organic damage in the arteriolar walls. In such cases, the blood pressure may establish itself at remarkably low levels considering the apparent severity of the acute disease. It is possible that some of the cases reported as examples of retinitis of acute nephritis really belong to this group.

The outlook for patients who have essential hypertension affords a striking example of the variability of the disease process. The present series of cases offers a good control for any specific form of therapy, as treatment consisted of general measures, especially with regard to diet and rest, and the regular use of certain sedatives. If the fact is considered that only nineteen patients, or 9 per cent, of our entire series

TABLE 2

Patients alive 5 to 9 years after first examination

HYPERTENSION GROUP	TOTAL PATIENTS	PATIENTS ALIVE		
		Male	Female	Total
1	10	4	2	6
2	26	4	5	9
3	37	2	1	3
4	146	0	1	1*
Total	219	10	9	19

* This patient was alive 11 years after first examination.

TABLE 3

Patients dead 5 to 9 years after first examination

HYPERTENSION GROUP	TOTAL PATIENTS	PATIENTS DEAD		
		Male	Female	Total
1	10	3	1	4
2	26	10	7	17
3	37	20	14	34
4	146	99	46	145
Total	219	132	68	200

of 219 were alive five to nine years after the diagnosis was made, the seriousness of the prognosis seems obvious. But, on further analysis, this grave outlook is more apparent than real, as a disproportionate number of the cases belonged in group 4. There are some patients in each group, and as many as 35 to 60 per cent in groups 1 and 2, that lived for a similar period of five to nine years. These facts

emphasize the significance of the original grouping, particularly from the prognostic standpoint, and also demonstrate that there are two predominating types of essential hypertension the relatively stationary or benign and the rapidly progressive or malignant type (tables 2 and 3)

TABLE 4
Deaths within a given number of years after first examination

YEARS	PER CENT			
	Group 1	Group 2	Group 3	Group 4
1	10	12	35	79
2	20	23	67	88
3	30	38	78	94
4	30	42	78	98
5	30	46	80	99

TABLE 5
Duration of life after first examination

HYPERTENSION, GROUP	TOTAL PATIENTS	DURATION OF LIFE	
		Median*	Mean†
		months	months
1	10	100 0	
2	26	63 0	
3	37	15 9	27 6
4	146	5 4	10 5

* The time in months after first examination during which 50 per cent of the patients in the group have died

† Can be calculated only for groups in which practically all of the patients have died, that is, groups 3 and 4

The prognosis for cases in group 3 and especially for cases in group 4, is very serious. Because many more males than females belong in these two groups, the death rate is much higher among males than females. A death rate within one year of 35 per cent in cases of group 3, and of 79 per cent in cases belonging to group 4, is in distinct contrast to that of 10 to 12 per cent in groups 1 and 2. The mortality in cases of group 4 approaches that found in certain forms of cancer

(table 4) In order to emphasize the difference in prognosis in the individual groups, survival curves as employed by statisticians were drawn (table 5;⁸ fig 43) The resulting curves are distinct for each of the four groups As might be expected, there is a gradual increase in the steepness of the curves from that of group 1 to that of group 4 These statistical findings give further support to the conception that there are different types of essential hypertension

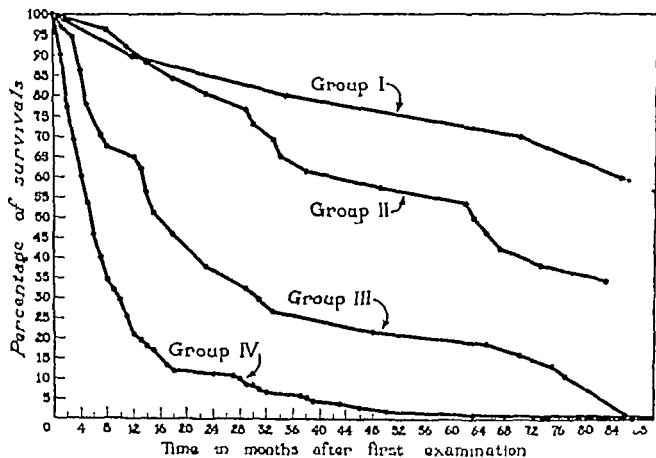


FIG 43 SURVIVAL CURVES FOR THE FOUR GROUPS OF DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION

MEDICAL TREATMENT OF ESSENTIAL HYPERTENSION

Since we know so little concerning the etiology of diffuse arteriolar disease with hypertension, methods of treatment are necessarily nonspecific No drug has been found which can compare in its beneficial action to that of digitalis in many types of myocardial failure Essential hypertension is far from uniform in its course, and this fact makes it difficult to appraise the value of any given therapeutic agent

⁸The authors are indebted to Dr J Berkson for making the necessary calculations for this table and chart.

In our experience certain measures appear to be helpful. The recording of the blood pressure every hour throughout a twenty-four hour period gives one information as to the effect of rest and sleep on the arterial system. In the so-called labile type of blood pressure the variations may be considerable and, usually, the lower readings occur during rest and sleep. Very often the patient who is free from symptoms sleeps well. That fact suggests the use of sedatives when rest and sleep are not easily attained. Chloral hydrate has a good record for helping hypertensive patients recover their former ability to sleep. Repeated small doses seem to have a better effect than larger amounts at longer intervals. The barbiturates, phenobarbital, pentobarbital sodium (nembutal) and sodium amytal, have proved useful. The last-named drug can often be administered in repeated doses by rectum with good effect. The caffeine derivatives that have proved to be useful in certain cases of coronary disease and peripheral arterial occlusive disturbances seem helpful in a limited number of cases of essential hypertension. Vasodilators, such as the nitrites and acetylcholine have only a transient depressor effect. Bismuth subnitrate has been used by Stieglitz because of the possibility of its being reduced to nitrite in the bowel and of a small amount being subsequently absorbed over a considerable period. He obtained some good results in cases that correspond to our cases of group 1. His results, however, have not been confirmed by Ayman (16). Actual chemical proof of a certain concentration of nitrite in the blood and a corresponding lowering of blood pressure would add strength to Stieglitz's claims, but so far such a relationship has not been conclusively demonstrated. Sodium and potassium sulfocyanate were introduced into the treatment of hypertension by Pauli in 1903. Others have confirmed his results, particularly Westphal and Gager, still other workers, however, have obtained no continued benefit. Serious toxic reactions, including severe skin lesions, have been reported (187). Barker has observed in several cases a significant decrease in levels of blood pressure together with symptomatic relief when the dosage was gauged by the level of cyanate in the blood. He found the optimal concentration for blood cyanates to effect a reduction in pressure to be 10 to 15 mg, and that toxic manifestations and vascular collapse have occurred at a level of approximately 50 mg per 100 c c. Further observation of

patients over a period of years is necessary to prove the efficacy of sulfocyanate in substantially reducing hypertension without causing toxic reactions

Certain physiotherapeutic measures have been advocated for lowering an increased blood pressure. These include high frequency current, diathermy, sweating procedures, and exposure to deep roentgen rays or radium. None of these has as yet been proved to cause a permanent decrease in hypertension. At The Mayo Clinic, Desjardins has subjected several patients belonging to groups 3 and 4 to roentgen therapy through paravertebral fields along the entire spine. One such patient appeared to be temporarily benefited but subsequently ran a downhill course and died. In one case, at necropsy, the kidneys showed evidence of diffuse and chronic hemorrhagic changes unlike those ordinarily seen in cases of this kind. At the time the possibility that their peculiar appearance might be due to irradiation was considered, but clear evidence of such a relationship could not be obtained.

The severe headaches, so troublesome in a considerable number of these cases, can sometimes be relieved by repeated drainage of the spinal fluid by means of spinal puncture. A striking result was obtained in one of our cases of hypertension after drainage of the spinal canal, three to four times within a week. The patient returned two years later and reported that he had been free from headache during the interval. When spinal drainage is ineffectual, headache can sometimes be alleviated by the use of hypertonic sugar solutions administered intravenously, such as glucose and sucrose. We have also found these hypertonic sugar solutions to be more effectual in some cases when acacia is added to a concentration of 3 per cent. The intravenous use of such solutions has also sometimes resulted in a decrease in the neuroretinal edema of patients belonging to group 4.

Certain general measures appear to be beneficial, particularly in the treatment of patients of groups 1, 2 and 3. These measures include moderation in the amount and kind of food ingested, regular hours of sleep, including a short midday siesta, and a daily warm bath. The use of graduated outdoor exercises, such as was advocated by Oertel in 1884 in the treatment of cardiac disease, seems to us to apply to some cases of diffuse arteriolar disease with hypertension. In

certain cases we, therefore, advise the equivalent of approximately two to three miles (3.2 to 4.5 km) of walking daily

There is as yet no satisfactory treatment for rapidly progressive diffuse arteriolar disease with hypertension. Control of certain nervous reflex mechanisms in which the sympathetic system is involved seems to offer an approach to this difficult problem. No satisfactory drug has been discovered which will produce such an effect. Recently, surgical operations on the sympathetic nervous system were devised with such an objective in view.

OPERATIONS ON THE SYMPATHETIC NERVES FOR THE TREATMENT OF HYPERTENSION

Adson and Allen (3, 4, 5) have stated that "There appear to be two factors in the elevation of blood pressure in hypertension (1) the inherent status of the arterioles and (2) abnormal reaction of the arterioles to vasomotor stimuli." In the earlier phases of essential hypertensive disease, or in those cases in which there are wide fluctuations of blood pressure, abnormal vasomotor response is probably the dominant factor. In the later phases of the disease, or in those cases in which the blood pressure remains at an essentially fixed high level, the inherent status of the arterioles is altered, apparently in part, at least, through organic changes in the walls of the arterioles, which may result from long continued increased vasomotor response. The source of the vasomotor stimuli is not definitely known, but they seem to be transmitted to the arterioles through the medium of the sympathetic nerves. Section of the sympathetic trunks leading to various organs or extremities prevents the transmission of these stimuli to the arterioles under this control. The rationale of the surgical approach to the treatment of essential hypertension lies in the presumptive value of interrupting vasomotor stimuli to various arteriolar beds.

The selection of the nerves or trunks to be sectioned varied considerably in the early phases of surgery for hypertension depending upon the individual investigator's conception of the probable cause of hypertensive disease. Thus Crile denervated the suprarenal glands because he felt that an increased secretion of epinephrine was the primary cause of hypertension. A temporary drop in blood pressure resulted, but no permanent effect on the course of the disease was

noted. More recently he has been removing the celiac ganglion with apparently better results. Because of the large vascular bed in the abdominal organs, with its recognized influence through relaxation and constriction upon the maintenance of normal arterial pressure, resection of the splanchnic nerves for the treatment of hypertension was suggested in 1923 by Daniélopou and in 1924 by Brünig and Stahl, and in 1925 by Pende. In 1925, Adson (6) performed ganglionectomy and trunk resection of the second, third and fourth lumbar ganglia on both sides in one case with the idea of producing a wider vascular bed in the lower extremities. Results, from the standpoint of lowering the blood pressure and controlling the disease, were not satisfactory. In this year, also, Adson performed unilateral cervicothoracic sympathectomy and trunk resection in a case of malignant hypertension with marked retinitis. No effect could be observed on the course of the retinitis.

In 1930, Adson (6) first performed rhizotomy of the ventral roots on both sides, from the sixth thoracic to the second lumbar segments, for essential hypertension, with excellent immediate results and more or less permanent reduction of the levels of blood pressure. About thirty such operations were performed. The effects of this operation on the hypertension were satisfactory in a considerable percentage of cases, but the operation required a long period of convalescence and was not universally applicable, since it was likely to be disabling in its after-effects in cases in which patients were engaged in more or less strenuous occupations.

Some type of splanchnic resection has become the method of choice at present for the surgical treatment of hypertension. The subdiaphragmatic approach of Adson and Craig would seem to be the preferable procedure since it not only makes possible resection of all three splanchnic nerves, but also complete removal of the first and second lumbar ganglia and partial removal of the celiac ganglion, thus producing vasomotor paralysis of a large arteriolar bed. This method of approach also permits inspection of the suprarenal glands and their partial removal if this seems indicated.

According to Fraclick and Peet, who tended to accept the experimental work of Goldblatt (88, 89) in the production of hypertension by constricting the renal arteries, the most important effect of splanchnic

resection is in the relief of renal vasoconstriction Adson and Allen (3, 4, 5) added that the improvement in the circulation through the kidneys may "aid in the elimination of metabolic products which, if present and retained as a result of disease of the kidneys, might perhaps produce pressor effects on the arterial tone" It would seem more likely, however, that the main effect obtained by the operation is the provision of a "reservoir in the denervated vascular area" when the undenervated vessels go into spasm, since Adson and Allen stated "Our experiences have shown that the best surgical results have been obtained when the operation has been extensive and a large vascular area has been denervated" The importance of this factor has been emphasized also by Fralick and Peet The accompanying denervation of the suprarenal glands should also prevent their reception of central influences, and the consequent dumping of epinephrine into the circulation under emotional stress Interesting evidence of the effect on the circulation produced by loss of vasomotor control in the splanchnic area is the marked fall in blood pressure, accompanied by tachycardia, which occurs when the patient assumes an upright position This is particularly noticeable during the period of convalescence, and it can be compensated for by the wearing of a tight-fitting corset

In 1934, the DeCourcys and Thuss (58, 59) presented their reasons for thinking that essential hypertension is caused by hyperplasia of the suprarenal glands, and they reported satisfactory results in six cases following removal of about two-thirds of each gland One patient was blind in the right eye as a result of hemorrhage into the retina The vision returned to normal following the operation The authors stated that the diastolic pressure usually remained below 100 mm of mercury postoperatively However, at the time of their report their cases had been followed for short periods only In two of their six cases, a small pleochrome tumor was found in a suprarenal gland

The three largest series of cases in which patients were operated on for the relief of essential hypertension in this country on which reports are available are those of Fralick and Peet, Page and Heuer, (183, 184) and Adson, Craig, Brown and Allen It is of interest in these series that a greater percentage of symptomatic than objective im-

provement was noted. The relief of headache is especially striking. Fralick and Peet reported the results for thirty-six of ninety operative cases studied from five to twenty-two months after operation. In five cases the blood pressure remained normal, in eighteen the blood pressure was appreciably lowered, and in thirteen the blood pressure remained at its preoperative level. A retinitis of the malignant hypertension type had resolved in two cases of the group in which the blood pressure had returned to normal, and an angiospastic retinitis had resolved in another case. The retinal changes showed improvement in only three of the eighteen cases in which the blood pressure was lowered and in only one of those in which the blood pressure was not lowered by the operation. Apparently, all types of cases were accepted for operation in this series except those with marked renal insufficiency.

In 1935, Page and Heuer reported the results of sectioning the anterior roots from the sixth thoracic to the second lumbar segment in a case of essential hypertension. The patient was a twenty-three year old woman whose blood pressure was 200 mm of mercury systolic and 140 mm diastolic. Following operation the blood pressure remained at almost normal levels for seven months, seldom rising above 160 systolic. In another case they performed bilateral denervation of the kidneys of a woman twenty-five years of age whose blood pressure was 200 systolic and 140 diastolic. No significant fall in blood pressure occurred. Page and Heuer thought that this experience made it doubtful that the nervous mechanism of the kidneys plays any rôle as a general rule, in the genesis of essential hypertension.

In a paper presented before the Academy of Medicine of Toronto in November, 1936, Heuer in association with Page, reported the results of twenty seven operations on the sympathetic nerves for the relief of hypertension. In nine cases, supradiaphragmatic resection of the major and minor splanchnic nerves combined with excision of the lower thoracic sympathetic ganglia was performed. Seven of the nine patients had mild benign hypertension, two malignant hypertension. In all cases the blood pressure promptly rose to its preoperative level and for periods of six months to a year continued at this level or became more elevated. In eighteen cases, the anterior roots from the sixth thoracic to the second lumbar spinal nerves were

sectioned on both sides According to Heuer, the results of this operation were much more satisfactory In fourteen cases, the immediate postoperative fall in blood pressure persisted for from one to two years, in four cases the blood pressure returned to its pre-operative level in from five to six months Four of five cases (80 per cent) of mild or moderately severe hypertension showed a satisfactory reduction in blood pressure averaging 24 per cent Of thirteen cases of severe and malignant hypertension, four (30 per cent) showed a fairly satisfactory fall in blood pressure (averaging 20 per cent), five (38 per cent) showed a less satisfactory drop in blood pressure (averaging 12 per cent) and four (30 per cent) failed to show any permanent reduction in blood pressure In none of the cases in this series did the blood pressure return to normal levels

Heuer stated that, in this series, "morbid changes in the eyegrounds when present before operation quite generally disappeared (109, 271) Relaxation of constricted retinal vessels, absorption of exudates and hemorrhages and reduction in the grade, or disappearance of the papilledema, were noted, not in all, but in many instances" He stated also that the enlarged heart decreased in size in a number of cases and that renal function was not changed as a result of the operation In summary Heuer stated that "Patients whose disease is benign without advanced morbid changes and young patients exhibiting signs of the hypertensive diencephalic syndrome are fairly certain to be greatly benefited by operation, patients with benign hypertension of long standing with marked arterial thickening form a more uncertain group from the viewpoint of results, while patients with malignant hypertension form a very uncertain group in whom the outcome of operation cannot at present accurately be predicted"

Adson and Allen (5) have stated "The operation (splanchnic sympathectomy) is most effective when applied to young individuals who have a progressive vasospastic type of hypertension, whose blood pressure rises markedly when the hands are immersed in cold water and who obtain a marked fall in blood pressure when pentothal sodium, amytal and nitrites are administered As a rule the patient must be less than forty years of age and his hypertension must be classed as of group 2 or 3" In general, the objective effects of the operation are that sudden and abrupt peaks of blood pressure will not

occur, the cold pressor tests produce lower levels of blood pressure, and the mean levels of blood pressure are lower. In the first series of cases reported by Adson, Craig and Brown in 1935, patients with all types of hypertension, including malignant hypertension, were operated on. Of twenty-seven cases in which extensive rhizotomy was carried out, the results were classified as good in thirteen cases, fair in six, and failure in six, with two postoperative deaths. Of forty-three cases, including rhizotomies, splanchnic resections and other types of operation on the sympathetic nerves, the results were classed as good in twenty cases, fair in nine and as failures in fourteen. The highest percentage of good results, five of seven cases, occurred in the group operated on by the subdiaphragmatic splanchnic technic mentioned previously. In the more recent series reported by Adson and Allen (5) of thirty-one patients operated on by this technic, the degree of reduction of blood pressure was classed as excellent in nine cases, good in eight, fair to poor in eight and as failures in six. General clinical results were good or excellent in twenty four cases. This group does not include cases of malignant hypertension.

In general comment on the results of splanchnic sympathectomy, Adson and Allen stated "The operation of splanchnic resection and removal of lumbar ganglions reduces the blood pressure and may cause disappearance of retinitis, may cause the inverted T-waves in the electrocardiogram to become upright, may decrease the size of the heart, may bring about a disappearance of the albumin from the urine and may relieve the symptoms resulting from hypertension.

It is also our opinion that the operative measures are most effective when applied to younger patients who are in the early stages of the disease, then vasospastic phenomena are readily demonstrable and irreparable damage has not been done to the cardiovascular renal system."

This last statement is borne out by our experience with the retinal changes in patients who have been operated on by those various technics. We have not observed any visible change in definitely organic lesions in the arterioles. On the other hand, angiospastic narrowings have been seen to become less marked or to disappear during convalescence, and angiospastic retinitis has subsided and has remained absent for at least a year following operation. The course

of localized venous thrombosis has not been influenced by surgery of the sympathetic nervous system. Close observation of these cases has given some clues to the differentiation of spastic and organic arteriolar lesions. It is apparent that if definite differentiation of these two conditions could be made with reasonable certainty in all cases, ophthalmoscopic examination would furnish a more valuable guide than it does at present in the selection of suitable cases for operation. Patients with retinitis of group 3 hypertension (angiospastic retinitis without edema of the disks) show a definitely better response to operation than do those with retinitis of group 4 hypertension (angiospastic retinitis with edema of the disks), although the postoperative course of the retinitis itself is about the same in the two groups. Thus of seven patients with retinitis of group 4 hypertension, the retinitis cleared up entirely in one case, was improved in three and was unchanged in three, and of twelve patients with retinitis of group 3 hypertension, the retinitis cleared up entirely in two cases, was improved in four, and was unchanged in five, and recurred shortly after operation in one. However, of the group of seven patients with hypertension of group 4, three (43 per cent) had died within six months after operation, while of the group of twelve patients with hypertension of group 3, two (16 per cent) had died within nine months after the operation. These statistics were based on the results in the first series of cases reported by Adson, Craig and Brown. A similar percentage of improvement in cases of retinitis of group 3 hypertension (approximately 50 per cent) has been noted in the later series of cases. It should be noted that, in a few cases, retinitis has shown an exacerbation in the immediate postoperative course or has appeared in cases in which angiospastic lesions were present without retinitis prior to operation. These exacerbations were always transient in character. The reason for this exacerbation or appearance of retinitis is not clear. The most logical explanation would seem to be that operations for hypertension hasten recovery in cases of retinitis which are in the receding phase, and are not immediately successful in altering the course of retinitis which is in its initial or rising phase.

In general summary of the indications for surgery on the sympathetic nervous system in cases of hypertensive disease, Adson and Allen said "Most patients who have hypertension, group 1, do not

require surgical treatment. Surgical treatment is advisable for patients who have hypertension, group 2 and group 3, if the hypertension is known to be progressive, if the function of the heart and kidneys is good and if the value of the blood pressures become normal or approximately normal as a result of rest or sleep, or following the intravenous injection of pentothal sodium, or following the administration of sodium amytal or the nitrites. Hypertension, group 4, does not respond satisfactorily to surgical treatment." Since it is not always possible to distinguish surely between the acute angiospastic retinitis with edema of the disks seen in patients with acute vasospastic hypertensive disease and that occurring in patients with hypertension of group 4 (malignant hypertension) it would seem worth while to determine the effects of surgery in a group of ophthalmoscopically doubtful cases in which the history suggests the possibility of an acute angiospastic episode rather than fixed progressive hypertension. It is now planned to perform splanchnic sympathectomy in such a group of cases.

SUMMARY

Since in the normal individual the volume and viscosity of the blood remain essentially constant, the general blood pressure is maintained at an average normal level through a rather delicate adjustment of the peripheral vascular bed as a whole to variations in demands for blood flow in local regions. This adjustment is accomplished mainly through regulation of the caliber or tone of the arterioles. Dilatation or contraction of the arterioles is accomplished, at least partially or at times, through the sympathetic vasomotor nerves, which are under the control of the vasomotor centers in the brain stem and also through reflex mechanisms within the vascular system itself, originating particularly in the carotid sinus and in the aorta. Probably also the caliber of the arterioles can be altered through an inherent mechanism in their walls without the necessary intervention of the sympathetic vasomotor nerves.

A pathologic elevation of blood pressure can arise from an increase in the volume or viscosity of the circulating blood or from increased cardiac output. These factors are found to be normal, however, in most cases of so-called essential hypertension. The rise of blood

of localized venous thrombosis has not been influenced by surgery of the sympathetic nervous system. Close observation of these cases has given some clues to the differentiation of spastic and organic arteriolar lesions. It is apparent that if definite differentiation of these two conditions could be made with reasonable certainty in all cases, ophthalmoscopic examination would furnish a more valuable guide than it does at present in the selection of suitable cases for operation. Patients with retinitis of group 3 hypertension (angiospastic retinitis without edema of the disks) show a definitely better response to operation than do those with retinitis of group 4 hypertension (angiospastic retinitis with edema of the disks), although the postoperative course of the retinitis itself is about the same in the two groups. Thus of seven patients with retinitis of group 4 hypertension, the retinitis cleared up entirely in one case, was improved in three and was unchanged in three, and of twelve patients with retinitis of group 3 hypertension, the retinitis cleared up entirely in two cases, was improved in four, and was unchanged in five, and recurred shortly after operation in one. However, of the group of seven patients with hypertension of group 4, three (43 per cent) had died within six months after operation, while of the group of twelve patients with hypertension of group 3, two (16 per cent) had died within nine months after the operation. These statistics were based on the results in the first series of cases reported by Adson, Craig and Brown. A similar percentage of improvement in cases of retinitis of group 3 hypertension (approximately 50 per cent) has been noted in the later series of cases. It should be noted that, in a few cases, retinitis has shown an exacerbation in the immediate postoperative course or has appeared in cases in which angiospastic lesions were present without retinitis prior to operation. These exacerbations were always transient in character. The reason for this exacerbation or appearance of retinitis is not clear. The most logical explanation would seem to be that operations for hypertension hasten recovery in cases of retinitis which are in the receding phase, and are not immediately successful in altering the course of retinitis which is in its initial or rising phase.

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pressure in these cases depends apparently on the increased resistance to blood flow in the periphery caused by a reduction in the capacity of the general arteriolar bed. In the early phases of the disease, at least, this reduction in capacity is the result of functional contraction of the arterioles rather than of structural changes in their walls, with a consequent decrease in lumen. Whether this contraction of the arterioles is due to increased stimulation of the sympathetic vasomotor nerves or to the direct action of a chemical or hormonal substance on the walls of the arterioles has not as yet been definitely demonstrated. The results of the cold test of Hines and Brown on hypertensive and prehypertensive individuals seemingly indicate an increased sensitivity of the arterioles to sympathetic vasomotor stimuli, which hypersensitivity may be inherited. However, the experimental studies of Pickering, Prinzmetal and Wilson, and of Goldblatt, point rather to a direct contractile response of the arterioles to some substance or factor in the circulating blood without the intervention of the sympathetic vasomotor nerves. When functional contraction of the arterioles persists or recurs at intervals for an indeterminate period, which varies considerably in different individuals, structural thickening of the walls of the arterioles is added apparently to the functional contraction as a factor in reducing the capacity of the arteriolar bed. This anatomic change in the walls of the arterioles, which is primarily a hypertrophy of the media, is observed most frequently or constantly in the arterioles of the kidney, but it is by no means confined to the kidney and it may be observed in many other organs and tissues such as the voluntary muscles, liver, capsule of the adrenal, pancreas, intestinal wall, brain, retina and choroid. It has been suggested that the anatomic lesions in the arterioles of the kidney are the primary site of origin of the disease syndrome of hypertension. No direct proof of this theory, however, is available. In the more rapidly advancing forms of hypertension, lesions are present also in the intimal endothelium of the smaller arterioles. It has been suggested that the presence of endothelial proliferation and intimal necrosis is the essential factor in determining the malignant course of the disease. On the other hand, however, these changes in the endothelium may be simply the response to more severe and persistent

functional constriction or spasm of the distal arterioles themselves or of the larger, more central arterioles

From the clinical standpoint, elevation of blood pressure occurs in cases in which there is obviously a primary lesion of the kidneys and also in cases in which no primary or secondary renal lesion can be demonstrated. In both these types of disease, the rise of blood pressure may occur acutely. In both, also, when the onset of hypertension is acute, there is often a tendency toward recovery. The blood pressure may return to normal or essentially so with little residual evidence of damage to the cardiovascular system. Such acute elevation of blood pressure may occur both in the acute, and more rarely in the chronic, cases of glomerulonephritis. In acute glomerulonephritis, hypertension may be very transitory and may be accompanied or followed by slight, if any, demonstrable damage to the arterioles. In chronic glomerulonephritis, the rapid onset of hypertension often ushers in the terminal phase of the disease, probably by intensifying the ischemia of the glomeruli. It is possible, however, for at least temporary recovery to occur in such cases. The occurrence of and recovery from such episodes can be observed in the retina in the form of acute angiospastic retinitis. When the blood pressure remains constantly and progressively elevated in chronic glomerulonephritis, it can be demonstrated both in the retina and elsewhere that a diffuse lesion of the arterioles is present which does not differ in any essential way from the diffuse arteriolar disease which is the characteristic feature of hypertension without demonstrable disease of the kidneys.

An acute or rapid onset of elevated blood pressure simulating that occurring in acute nephritis can be observed both in the hypertensive toxemias of pregnancy and in the acute vasospastic hypertensions of previously normal individuals. In either of these two types it is possible for complete recovery to occur. In the majority of such cases in the nonpregnant, however, and in some of the cases associated with pregnancy, a certain amount of anatomic damage remains in the walls of the arterioles and hypertension persists in a more chronic and less progressive form. The acute angiospastic lesions occurring in the retina of patients in these two groups are especially noteworthy.

In hypertension of the so-called essential type, two large groups of cases are readily differentiated and their existence is now quite generally accepted. The "benign," essentially nonprogressive hypertension, or hyperpiesia of Clifford Allbutt, was the first to be recognized and constitutes perhaps the largest group of cases of clinical hypertension. The rapidly progressive or "malignant" hypertension has also been quite clearly defined and differentiated from the terminal phases of chronic glomerulonephritis which it simulates in some cases. In "benign" hypertension the retinal lesions are confined to the arterioles and are relatively minimal in degree. In "malignant" hypertension, angiospastic ("albuminuric") retinitis with edema of the disks is invariably present. Between these two extremes, however, exist cases in which severe structural changes in the walls of the arterioles or the recurrence of mild angiospastic episodes can be demonstrated especially by the lesions in the retina. The presence of either of these factors makes the prognosis for the life of the patient more serious than in the "benign" group, though less serious than in the "malignant" group. It seems possible, therefore, from the standpoint of prognosis at least, to divide cases of "essential hypertension" into four groups, for the present best designated by numbers instead of names. In the first two groups the lesion in the arterioles is essentially anatomic, perhaps residual to previous angiospastic episodes or else evolving as the result of long-continued increase in arteriolar tonus without active angiospastic episodes. In the last two groups, the essential lesion in the arterioles is active spastic constriction superimposed either on increased arteriolar tonus or on anatomic thickening of the walls of the arterioles, or on both. Whether the disease runs a truly "malignant" or a somewhat less rapid course would seem to depend on the diffuseness or persistence rather than simply on the degree of the angiospasm, on the possibility of elimination of the causative spastic agent, and to a certain extent on the adaptability of the vascular system of the individual. To date no form of therapy has proved very efficient in the control of the more progressive forms of hypertensive disease. From the medical standpoint, judicious regulation of rest, exercise and sedation have proved seemingly to be as successful as any of the so-called specific drugs. Various types of surgical operations on the sympathetic system, par-

ticularly splanchnic resection, have been found to lower blood pressure at least for certain periods. But, as in the case of medical therapy, surgery has obtained its best results in the milder or more chronic cases. It has not been demonstrated as yet that surgical intervention can essentially alter the course and prognosis in cases of hypertensive disease of the more rapidly progressive or malignant type

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PROPERTIES OF VIRUSES*

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The word "virus" was originally used only in the singular and meant a poison such as snake venom. Later, with the establishment of a difference between poisons and infectious agents, the word virus was usually used only in connection with the latter entities. However, following Beijerinck's confirmation in 1898 of Iwanowski's earlier observation that the juice of mosaic-diseased plants remained infectious after being passed through a Chamberland filter and his realization that the infectious entity differed from ordinary bacteria, the word virus was applied only to those infectious agents capable of passing filters that retained ordinary bacteria. With time, difficulties arose, for bacteria like entities, such as the pleuro-pneumonia organism, were found to pass filters which retained agents which appeared to be viruses. For a short period of time the word virus was used in connection with such filter-passing organisms, but within the past few years there has been a further narrowing of the definition so that recently properties ascribed to viruses included not only their ability to pass fine membranes but also a set of general properties which emphasized especially the intimate relationship that exists between viruses and their host cells. These include the fact that viruses reproduce, but do so only within certain living cells, the fact that during reproduction they may change or mutate, or that they may be caused to change or mutate, the fact that many virus-infected cells contain inclusion bodies, and the fact that most, but not all, virus diseases are followed by a lasting immunity in recovered hosts. It should be emphasized that viruses have been described almost entirely in terms of their biological activity. They were first recognized and continue to be recognized only by means of this activity.

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Until recently, but little work had been done on the chemical and physical properties of viruses and their general nature was quite unknown. An element of mystery tended to surround them, for they were regarded as different sorts of infectious disease-producing principles and, with the exception of certain viruses of the elementary body type, attempts to isolate a virus in tangible form had resulted in failure.

However, three years ago at the Congress in London, I reported the isolation from mosaic-diseased Turkish tobacco and tomato plants of a high molecular weight crystalline protein possessing the properties of tobacco mosaic virus, and of two additional crystalline proteins of high molecular weight possessing, respectively, the properties of a masked and of a yellow strain of tobacco mosaic virus. Because of the widespread doubt concerning the significance of these materials, but more especially in order to emphasize their protein nature, they were referred to at the time as virus proteins although, as will be pointed out in a few moments, there now appears to be ample reason to refer to them merely as viruses. The isolation of the high molecular weight materials was immediately confirmed in several laboratories and was soon followed by the isolation by the same or similar chemical methods or by means of differential centrifugation of over 20 similar high molecular weight materials possessing some of the properties of the respective viruses or virus strains. Of these, Bawden and Pirie have isolated enation mosaic virus, which is a strain of tobacco mosaic virus, cucumber mosaic viruses 3 and 4, which are also related to tobacco mosaic virus, potato Y virus, and the very interesting bushy stunt of tomato virus, Wyckoff and I have isolated the tobacco ring spot, severe etch, cucumber mosaic 1, and latent mosaic viruses, the latter of which has been studied more extensively by Loring and by Bawden and Pirie. Beard and Wyckoff obtained the Shope papilloma virus, Wyckoff the equine encephalitis virus, Schlesinger a coli bacteriophage, Northrop a staphylococcus bacteriophage, and Claude the Rous sarcoma virus as materials of high molecular weight. Recently Pirie, Smith, Spooner, and McClement isolated tobacco necrosis virus and Janssen the foot-and-mouth disease virus in the form of heavy nucleoproteins. Reports of the isolation or the presence of material of high molecular weight in preparations of still

other viruses are being made from time to time. For example, other than additional work on some of the viruses just mentioned, during this Congress Bauer and Pickels have reported on yellow fever virus, Clark on poliomyelitis virus, and Furth and Kabat and Pentimalli on fowl leukemia virus.

Now, it may be well to pause a moment and examine critically the status of the work with these different materials of high molecular weight. In every instance the preparations not only have possessed virus activity but have had an activity greatly increased over that of the starting material. In every instance, therefore, concentration of the virus has been achieved. However, are we justified in assuming that the maximum concentration has been achieved in every instance, that is to say, that the different preparations are essentially homogeneous and hence represent the different viruses in an essentially pure condition? At the present time the answer must be in the negative, for in some instances the only criterion of purity has been the fact that the active agent could be sedimented in a high speed centrifuge, and in other instances that the active material was homogeneous in the Svedberg centrifuge or in the Tiselius electrophoresis apparatus. As you know, it is difficult, if not impossible, to prove conclusively that any given material is pure. However, the chemist usually approaches such a problem by testing the homogeneity of the preparation by all known methods and, failing to obtain any evidence of inhomogeneity, he is then willing to conclude that the substance is pure. It should be emphasized, however, that such a conclusion is not warranted until all known methods have been utilized and have failed to reveal the presence of an impurity, for it is quite possible that an active agent and an impurity might sediment in a centrifugal field or migrate in an electrical field, for example, at exactly the same rate and hence appear as one by these tests, but it is extremely unlikely that all of the chemical and physical properties of the active agent and an impurity would be exactly the same. In most of the cases of the 20 or more purified virus preparations that have been obtained, only one or two tests for homogeneity have been applied, and it would be, therefore, extremely hazardous to base a conclusion regarding purity on such scanty data. Is it necessary, on the other hand, to conclude that the data on the 20 or more purified viruses

are entirely without significance? One might be justified in adopting such an extreme viewpoint if there were no order or relationship between the various preparations. However, it has been obvious for some time, because of the work of Elford and others on the filtration of viruses, that one would expect to obtain, on isolation of the different viruses in purified form, preparations composed of discrete particles of sizes characteristic of the respective viruses. In other words, with respect to size one could have anticipated to a certain extent what has been found in the cases of these purified preparations. If, in addition, it should prove to be possible to subject, with negative results, one or two of the representative purified virus preparations to a sufficient number of different tests for homogeneity to warrant the conclusion that they are essentially pure and hence the viruses, then less complete data on the remaining virus preparations should take on an added significance. In fact, even a few tests indicating homogeneity could then be considered as good presumptive evidence that the preparation is essentially pure and consists of virus.

It becomes of considerable importance to virus work in general, therefore, to examine the available data critically in order to determine whether or not sufficient experimental results are available in connection with any one virus preparation to justify the conclusion that it is homogeneous and hence actually consists essentially of virus alone. As many of you know, there are tremendous experimental difficulties which obstruct extensive work with most of the viruses, for example, they may be very unstable, they may occur in their hosts in very low concentrations, or it may be difficult to secure large amounts of starting material. Fortunately, there are a few viruses which are not attended by such handicaps and one of these, namely, tobacco mosaic virus, has been subjected to extensive investigations in several laboratories during the past four years. The material which has always been isolated from mosaic-diseased plants has been found, with few exceptions, to have quite definite and constant chemical, biological, immunological, and physical properties. Available data indicate that it is a conjugated protein, containing 95 per cent protein, 5 per cent nucleic acid, and no lipid. It has been found to yield only amino and nucleic acids on hydrolysis. Dr Loring has demonstrated not only that the latter is a true nucleic acid by the

isolation of guanine, cystosine, adenine, and uridylic acid, but also that it differs in certain respects from all known nucleic acids. The amino acids which have been identified by Dr. Ross include arginine, aspartic acid, cysteine, glutamic acid, leucine, lysine, phenylalanine, proline, serine, tyrosine, and tryptophane. Alanine, histidine, and glycine are either absent or occur in amounts that have not been measurable. Except for the absence of histidine, there is nothing especially unusual in the amino acid composition of the material. Because of the interest in Kögel and Erxleben's demonstration of the occurrence in cancerous tissue of glutamic and other amino acids having markedly lower optical rotations indicative of the presence of the unnatural isomers, it should be mentioned that Dr. Ross has found the glutamic acid of the virus material to be the naturally occurring d-glutamic acid. The nucleoprotein contains 50 per cent carbon, 7 per cent hydrogen, 16 per cent nitrogen, 0.24 per cent sulfur probably in the form of sulfhydryl sulfur, and 0.6 per cent phosphorus. It is isoelectric at pH 3.5 and has a density of 1.37, a sedimentation constant of 174×10^{-13} cm. sec.⁻¹ dyne⁻¹, a diffusion constant of 3×10^{-6} cm.²/sec., and a rotational diffusion constant of 25 sec.⁻¹ at 0°C. It is completely homogeneous in the Svedberg centrifuge and in the Tiselius electrophoresis apparatus. Particles of the material are remarkably asymmetrical, and its solutions exhibit double refraction of flow, electrical double refraction, and on standing tend to separate into two layers the lower of which is spontaneously doubly refracting and the upper of which shows double refraction only when caused to flow. Using indirect methods, Lauffer and I have estimated that the molecules of the nucleoprotein are about 400 m μ in length and about 12 m μ in cross section. Recently, by direct observation by means of the electron microscope, Kausche, Pfankuch, and Ruska demonstrated that most of the molecules in a dilute solution of a chemically prepared sample were about 300 m μ in length and about 12 to 15 m μ in cross section. However, evidence of marked aggregation of particles in more concentrated preparations was obtained by this method. The material gives a beautiful X-ray diffraction pattern which Bernal has interpreted as being due to rods about 15 m μ in cross section, having an internal regularity which might be considered as crystalline and when concentrated arranged in liquid or in solid

form with a perfect hexagonal 2-dimensional regularity at right angles to the length but with no regularity in the direction of the length of the rods. The material gives specific precipitin and anaphylaxis reactions and, when highly purified, it is impossible to detect the presence of extraneous substances by immunological tests.

Of great significance is the fact that the virus activity of preparations having the chemical and physical properties or constants just described is also essentially constant regardless of the source of the starting material. Tobacco mosaic virus has one of the widest host ranges known, for 46 different species of plants representing 14 widely separated families are susceptible to the disease. Yet, whether isolated from diseased tobacco, tomato, petunia, or phlox plants, the virus activity per unit of nucleoprotein does not vary significantly. It is possible, of course, to obtain preparations of lower activity by treatment with deleterious agents, such as acid, alkali, or heat, or by prolonged exposure to strong salt solutions. As a matter of fact, some of our first preparations and many of the samples prepared in other laboratories were injured by the very processes used for isolation and had greatly lowered activities. However, if caution is exercised, it is not difficult to secure preparations having a high and constant activity. The total activity of these preparations does not differ by more than about 20 per cent from that of the samples of the untreated infectious juice of frozen mosaic-diseased Turkish tobacco plants used as starting materials. There is, therefore, good reason to believe that the virus activity of such preparations has not suffered as a result of the purification process. The isolation of many preparations having the same high and constant activity from many different batches of starting material from the same and from different hosts was, of course, good presumptive evidence that in every case the same material was being obtained.

Of greater significance, however, are the results obtained in a series of studies in which the virus activity was correlated with physical and chemical properties. In every case yet studied, treatment which has caused changes in one or more of the chemical or physical properties of the material has also caused a change in virus activity. Digestion with certain enzymes or denaturation by acid, alkali, heat, dodecyl sulfate, urea, etc., causes loss of activity, and in general the

rate of digestion or of denaturation and the rate of loss of activity have paralleled each other. The inactivation of the preparations by formaldehyde has been studied in great detail by Dr. Ross, and he found not only that the inactivation was accompanied by a decrease in amino nitrogen, but more important that the reaction could be reversed and that the reactivation was accompanied by an increase in amino nitrogen. The ultraviolet light absorption spectrum of the material has been found to be essentially the same as the destruction spectrum of virus activity. In a variety of experiments it was found impossible to alter the activity by fractional crystallization, precipitation, filtration, or diffusion, or by centrifugation of negatively charged, positively charged, or neutral nucleoprotein, or by means of centrifugation from mixtures with various other materials. In recent unpublished work, Dr. Loring found that the solubility of the ultracentrifugally isolated nucleoprotein varied only slightly with a large change in the amount of solid phase present, a result indicative of unusual homogeneity. During the past four years, much of the work in my laboratory has been devoted to a study of the homogeneity of this high molecular weight material isolable from tobacco mosaic diseased plants, yet in all of this work and in all of the work which has been reported from other laboratories, not a single bit of experimental evidence has been obtained that is incompatible with the idea that this material is actually tobacco mosaic virus in an essentially pure form. It would seem, therefore, that we are in an excellent position to make a decision regarding the homogeneity of this nucleoprotein. However, before doing so there are two points that I should like to consider. In the first place, with this material, as must always be the case with any material, it is possible that a property, in this case the virus activity, may be due to something which has not been comprehended as yet. Since this possibility must always remain, I think we should remember it, but because of the great mass of experimental data now available, we should relegate it to the background. The second point is, because of the fact that the production of virus is accompanied by mutation and hence by the simultaneous production of at least small amounts of closely related strains, it seems likely that despite the tests indicative of homogeneity the material actually consists of a family of closely related nucleoproteins. However, it would

appear that most of a given preparation consists of identical structures and the remaining small amount consists of structures so closely related that the difference is not detectable by ordinary means. Although the possibility of this situation should be recognized, it cannot alter the validity of the experimental results, and I think, therefore, that on the basis of evidence now available we are justified in concluding that for all practical purposes the nucleoprotein preparations consist of essentially pure and homogeneous tobacco mosaic virus.

In connection with the other purified virus preparations, it should be noted that it has already been possible to demonstrate that the purified preparations of the different viruses have quite different and highly characteristic chemical, physical, and serological properties. The properties of preparations of strains of a given virus have been found to be somewhat similar, although in every case so far studied differences have been found. Furthermore, the amounts of the purified materials have been found to vary tremendously depending upon the virus or virus strain as well as upon the host. Because of these and other experimental data and because it has been possible to conclude that tobacco mosaic virus has been obtained in essentially pure form it appears that we are now in a position to make at least some tentative conclusions regarding other virus preparations. Although they have been studied to a lesser extent, it appears that in the cases of the four other strains of tobacco mosaic virus, the related cucumber mosaic 3 and 4 viruses, latent mosaic of potato virus, and the staphylococcus bacteriophage there is good reason to believe that the respective active agents have been obtained in pure form. There is also good evidence that the preparations of tobacco ring spot and bushy stunt of tomato viruses are essentially pure, and fair evidence that the Shope rabbit papilloma and foot-and-mouth disease viruses have also been obtained in essentially pure form. Although in the cases of the remaining purified virus preparations the extreme instability of the virus, the isolation of similar preparations from normal tissues, or the known presence of extraneous substances have cast some doubt upon the significance of the results, it seems obvious that, with varying degrees of certainty depending upon the individual case, a great variety of viruses have been obtained in an essentially

pure form Some of these are viruses affecting plants, whereas others are viruses affecting animals, yet they have been grouped together This has been done knowingly, for it seems likely that virus activity, whether it be manifested in plants or in animals, is fundamentally the same, hence, there is no valid reason for separating the viruses affecting plants from those affecting animals Information gained from the plant side should be used to supplement that gained from the animal side, and *vice versa*, without discrimination Some of these viruses, such as those of tobacco mosaic and its strains and those of the related cucumber mosaics 3 and 4, are conjugated proteins containing about 5 per cent nucleic acid, others such as tobacco ringspot contain about 40 per cent of nucleic acid, others such as latent mosaic contain nucleoprotein plus additional carbohydrate, and still others appear to contain not only nucleoprotein plus additional carbohydrate but also some lipoid, although the necessity of the presence of lipoid in a virus has not been definitely established as yet The sizes of the purified viruses have been found to correspond closely to the sizes previously estimated by Elford and others from filtration data on unpurified or on semi purified preparations, although in some cases the estimates have been revised downwards

One important result of the purification work was the finding that viruses differ tremendously in shape Tobacco mosaic virus, its strains and related viruses, and latent mosaic of potato virus are long, thin rods, whereas tobacco ringspot, bushy stunt, and the Shope papilloma viruses appear to be essentially spherical in shape The demonstration that tobacco mosaic virus consists of long rods and the probability that treatment with salt or other agents causes two or more of these rods to combine end to end, to a certain extent irreversibly, with the formation of still longer rods has permitted a rational explanation of the rather puzzling filtration behavior of this virus As many of you know, tobacco mosaic virus has been reported to have a filtration end point varying all the way from about 13 $m\mu$ to over 300 $m\mu$, depending upon the conditions and preparations used Bawden and Pirie found, for example, that their purified virus would not pass filters having an average pore size of 450 $m\mu$ We have, however, established that the filtration behavior of ultracentrifugally purified virus does not differ essentially from that of the

virus in untreated infectious juice. If such purified virus, which will of course readily pass a membrane of average pore size $450\text{ m}\mu$, be treated with ammonium sulfate, it becomes sufficiently aggregated so that following removal of the salt the virus will no longer pass the filter. As is well known, our theories of filtration are based upon spherical particles and, since similar theories for rod-shaped particles have not been worked out as yet, the filtration data on viruses known to be rods must be interpreted with caution.

The unusual shape of tobacco mosaic virus has also resulted in some interesting observations on its solutions which are considered as experimental proof for the existence of long range forces acting between the individual particles. In the past, the forces between molecules in solution have been regarded as being effective only over relatively short distances of a very few \AA units. However, in our various theories of the mechanism by means of which viruses reproduce, and, for that matter, in our theories of other intracellular events, it has been necessary to postulate the existence of forces acting over considerable distances, and it has been a matter of some embarrassment that the actual existence of such forces has been denied on theoretical grounds. Within the past year, Langmuir in this country and Levine in England have, almost simultaneously, shown that there are good theoretical grounds for believing that forces between molecules may act over distances as great as several hundred \AA units. Bernal has shown by means of X-ray measurements that in the lower doubly refracting layer of solutions of tobacco mosaic virus, where the molecules are arranged in a hexagonal close-packed lattice of parallel rods, the distance between the adjacent molecules may vary continuously from about 125 to 500 \AA , depending only upon the concentration of the solution. This striking demonstration of the existence of forces acting between molecules hundreds of \AA units apart, and their acceptance from the standpoint of theory alone, are of considerable importance, for we are now justified in using such forces in a tentative portrayal of the mechanism of virus action, such as the one which I presented two years ago at the meetings of the American Association in Indianapolis. If there are forces by means of which one molecule can cause a certain definite orientation of another molecule hundreds of \AA units away, then does it seem unreasonable to suppose, as was done two years ago, that the molecule may also cause the orientation

and alignment of sub-units at a distance, which when completed is followed by the combination of these units, inasmuch as such combination represents a stable form? This picture may appear far too simple, but it seems to me that it must be essentially correct and that it should not be complicated at this time by reference to the numerous catalytic reactions which probably serve as its foundation

Now, you may well ask what is it that has been denied other materials and given to the viruses which enables them to utilize these forces in the reproduction of their kind Why should an egg albumin molecule or, for that matter, formolized tobacco mosaic virus, which must certainly be affected by long range forces, not be able to reproduce? I do not know, but I am convinced that the answer must lie within the structures which are characteristic of these materials We are faced with many similar problems in organic chemistry Why should a relatively inert anthracene molecule to which has been added a few sub groups suddenly become a potent carcinogenic agent, which on further slight change may become a female sex hormone, which on additional slight change may become the male sex hormone, and so on almost endlessly Although the reason why a certain structure should be accompanied by a given activity remains a secret, it has been demonstrated that given structures are accompanied by given biological activities No such remarkable achievement has been accomplished with the viruses, yet, despite their apparent diversity, there must be some characteristic structure which endows them with their biological activity There are, however, certain leads, perhaps the most significant of which is the fact that all viruses appear to be or at least to contain nucleoproteins The ability of organisms to reproduce is associated with nuclear material, and we assume that the basic unit of this material is a gene, perhaps a single nucleoprotein molecule We know that the makeup of at least one virus, namely, tobacco ringspot virus, must be very similar to such material, for it has been found to contain 40 per cent nucleic acid and 60 per cent protein, a ratio practically the same as that found in the purest nuclear material readily available to chemists, the nucleoproteins which make up fish sperm The properties of the viruses composed of nucleoprotein are, so far as I can see, essentially the properties which we would postulate for a gene or for a group of genes, were they capable of an independent existence It may be,

therefore, that in the viruses we have a structure fundamentally the same as that which may be considered to characterize genes but which has been further adapted to an independent existence

The possibility of this structural relationship is of great importance in genetics, for the studies which can now be made on virus reproduction and mutation may have a direct relationship to similar events within cells. Furthermore, the characteristic structure which permits a virus to enter into the metabolic chain of events within cells may have a direct bearing on the advent of cancerous growths, a close relationship between the Shope papilloma virus and certain cancers already having been proved experimentally by Rous and coworkers. The fact that the change in structure brought about by the mutation of a virus may be accompanied by a marked change in biological activity and the fact that some strains of a virus may be so mild that they may persist almost unnoticed in a host whereas other strains of the same virus may have a severe effect on the host may also be of importance in the aetiology of certain cancers. There is, therefore, every reason to pursue with the utmost vigor the problem of the nature of the structure resulting from a combination of amino and nucleic acids which is characterized by virus activity. There is no reason why this problem should be shrouded in a veil of vitalism for the chemical, biological and physical properties of matter, whether atoms, molecules, germs or cells are directly dependent upon the structure of matter, and the results of the work with viruses have permitted the conclusion that the nature of this structure is fundamentally the same regardless of its occurrence. It seems to me that as structures become increasingly more complex, the only difference is that the additional complexity permits of more complex expressions of that structure, and that there is in reality a continuum from simple to complex structures, from molecules to organisms, and that after all there is no great difference between the two. Therefore, the all-important and fundamental problem of virus activity, with which may be associated questions of great importance in genetics, pathology, immunology, biology, theoretical physics, and allied fields, is one of chemical structure. It is a straightforward problem of structural organic chemistry, and, although it may appear at present to present unsurmountable difficulties, I am confident of its eventual solution.

MYOTONIA

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HISTORICAL INTRODUCTION

In 1833 Bell (9) described under the heading of "affection of the voluntary nerves" a condition in which the "consent of the muscles" was imperfect. Affected individuals, although capable of great bodily exertion and suffering from "no irresolution in the motion of the limbs when at ease or under a flow of spirits," were unable at times, especially under excitement or fright, to put one leg before the other and would stagger like drunken men. This appears to be the earliest reference to the disease which Thomsen (139) described in 1876 and which now bears his name. Thomsen, who suffered from the disease himself, described the "tonic cramp condition" which occurred in the muscles on voluntary contraction and subsided only gradually. He described the onset in childhood, the involvement of most of the muscles of the body, and the hereditary nature as seen by its occurrence in many members of his family through several generations.

In 1881 Strumpell (137) suggested that this "well characterized and easily recognized" condition be called "myotonia congenita." Erb (41), in his monograph in 1886, accepted and thus established the name of myotonia congenita for the disease described by Thomsen. The muscle disturbance characteristic of the disease became known as "myotonia," and the reaction of the muscles to mechanical and electrical stimulation was called by Erb "the myotonic reaction."

Following recognition of the disease, atypical cases were recorded in which the myotonia set in late in life, or had a very limited distribution, or was associated with atrophy (*myotonie atrophique* of Rossolimo (114)) instead of the previously reported hypertrophy. In 1909 Batten and Gibb (7), and independently Steinert (135) recognized that most of these cases represented a different malady in which, in contrast to myotonia congenita, the myotonia was limited in distribution and associated with a characteristic pattern of muscular atrophy. In 1912 Curschmann (32) recognized the significance of the extramuscular symptoms—the cataract, testicular atrophy, baldness,

and others—and called this disease “dystrophia myotonica.” Fleischer (48) in 1918 stressed the hereditary features of the disease

Until very recently neither dystrophia myotonica nor myotonia congenita has received much attention in American literature The

TABLE 1

Muscular Atrophy	Idiopathic	Sporadic	Myopathic	Amyotonia Congenita (Oppenheim)
			Myelopathic	Progressive Muscular Atrophy (Aran Duchenne) Amyotrophic Lateral Sclerosis (Charcot)
		Hereditary	Myopathic	Myasthenia Gravis (Wilks Erb) Family Periodic Paralysis (Cavare) Progressive Muscular Dystrophy (Erb Landouzy) Myotonia Congenita (Thomsen) Dystrophia Myotonica (Deleage)
				Infantile Muscular Atrophy (Werdnig Hoffmann)
			Myelopathic	Hypertrophic Neuritis (Dejerine-Sottas)
				Peroneal Muscular Atrophy (Charcot Marie Tooth) Familial Ataxia (Friedreich)
	Secondary	Disuse Trauma Tabes Dorsalis Neuritis Virus Bacterial Bacteriotoxic Toxic Vitamin deficiency, etc. Pollomyelitis Acute Chronic Syphilis Lead, etc.		

position among the myopathies of myotonia congenita and dystrophia myotonica is shown in table 1 (modified from Aring and Cobb (5)) Dystrophia myotonica is apparently much more common than myotonia congenita and, as judged by recent reports, can hardly be considered a rare disease Because of the presence of the striking

phenomenon of myotonia, these conditions are readily diagnosed if kept in mind, but the general unfamiliarity of practitioners with myotonia leads frequently to incorrect diagnosis. The purpose of this paper is to describe myotonia, its characteristics, its reaction to drugs, its nature, and its occurrence.

Myotonia may be associated with contractions produced by nerve impulses, mechanical stimuli or electrical stimuli. It is most commonly seen in voluntary contractions, that is, contractions produced by nerve impulses.

MYOTONIA ASSOCIATED WITH CONTRACTIONS PRODUCED BY NERVE IMPULSES (ACTIVE OR VOLUNTARY MYOTONIA)

1 Persistence of contraction after cessation of the nerve impulses

Normally the state of contraction of a muscle ends in an abrupt manner a small fraction of a second after the cessation of the stimulus producing the contraction (49). In a muscle exhibiting myotonia the state of contraction does not stop suddenly shortly after the cessation of the stimulus but persists for an abnormally long time and subsides only gradually.¹ This persistence of the contraction appears as a slowness in the return of the muscle to its original length. Since the return of the muscle to its original length after cessation of the forces producing contraction is a passive process depending on the presence of an outside extending force, the abnormality in myotonia is a persistence of the state of contraction rather than a delay in the passive process of relaxation. Insofar, however, as relaxation ordinarily occurs upon the cessation of voluntary effort, it is convenient to speak of a delay of relaxation in myotonia.

The abnormal persistence of the contraction can be felt and indeed seen when the muscles lie superficially. The muscle which at rest is of about normal firmness and resiliency becomes on contraction markedly firm and remains so for many seconds. The abnormality can, however, be studied more carefully by means of kymograph records. In these it is seen that only occasionally does the contraction persist at its full extent for even a short time. When the myotonia is marked,

¹ This statement implies a peripheral origin of myotonia. The evidence for this will be given later.

relaxation may be slow from the start. More frequently a period of fairly rapid relaxation is followed by a period during which the contraction subsides more slowly (see below for explanation). The initial period may be normally rapid and a sudden catch with angle

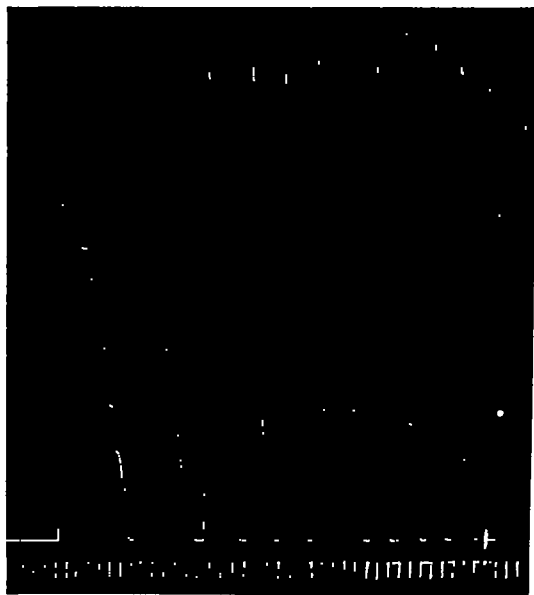


FIG. 1. RECORD OF THE CONTRACTIONS OF THE THUMB OF A PATIENT WITH DYSTROPHIA MYOTONICA

Upstroke represents contraction of the myotonic muscles. The degree of myotonia is indicated by the prolongation of relaxation (downstroke). Note the decrease in myotonia with each repetition of the contraction and the 'catch' as the rapid phase of relaxation changes to the slow phase.

formation occur at the start of the slower period (fig. 1). The period of slow relaxation may be smooth, showing a gradual and steady subsidence of the contraction or it may be step-like.

The duration of the myotonic contractions may be from a fraction of a second to over a minute depending on the extent of involvement.

of the muscle and the strength of the contraction. The majority last less than a minute and reported contractions of several minutes duration are probably either grossly over-estimated or are not true cases of myotonia.

Myotonia is not associated with pain. "Stiffness" and occasionally "tension" may be complained of, but almost never pain. This absence of pain is of great importance in distinguishing myotonia from other conditions which may simulate it, such as the muscle cramps associated with irritative nerve lesions.

Clinically, persistence of contractions is strikingly shown in many ways. After grasping an object the person afflicted with myotonia may be unable to release the object for many seconds. A stiffness may occur in the jaws during mastication, in the knees after squatting, or in the legs on starting to walk. If the eyelids are strongly closed, they often cannot be opened immediately, and after looking suddenly to the side, the eyes may remain fixed for many seconds.

2 Voluntary origin of the nerve impulses

The myotonic contractions produced by nerve impulses are, with few exceptions, voluntary contractions, hence the name "active or voluntary myotonia." Prolonged involuntary contractions, such as those which occur in tetany or in some lesions of the nervous system must be carefully distinguished from myotonic contractions which they usually resemble only superficially. The occurrence of such involuntary contractions in a myotonic patient is an adventitious and uncommon event. In addition to their involuntary nature these contractions do not show the other distinguishing characteristics of myotonia to be mentioned. Resistance to passive movement such as is commonly found in lesions of the central nervous system does not occur in myotonia nor does passive movement result in a myotonic contraction.

Difference of opinion exists on the occurrence of myotonia following reflex movements. It has been reported that during reflex activity, such as coughing, the latissimus dorsi contracts normally, while during voluntary activity it exhibits myotonia (47, 58, 70, 133). On the other hand, myotonia of the chest, stomach, and eye muscles may at times be observed following marked reflex movements such as cough-

ing, sneezing or hiccoughing (53, 113, 137) Stretch reflexes, such as the knee jerks and biceps reflex, appear to occur with normal rapidity. As will be noted later, a certain strength of contraction is often necessary for myotonia to manifest itself, and it is probable that whether or not a muscle will show myotonia on reflex contraction will depend on the intensity of the reflex and strength of the contraction. This conclusion is supported by the evidence to be given that myotonia is due to a change in the muscle. Contractions associated with tendon reflexes are probably too brief and too weak for the production of myotonia of demonstrable degree.

Under the influence of cold, slow spontaneous contractions occur in paramyotonia, a related condition. Occasional statements of patients with myotonia suggest that cold may at times produce spontaneous persisting contractions, thus, a patient told the author that in marked cold his chin muscles "puckered up." Bürger and Shellong (23) report the production of a persisting contraction in the biceps by the use of an ethyl chloride spray.

3 Decrease with repetition of the contraction

Probably no true exception exists to the statement that in a series of contractions following a period of rest, myotonia diminishes in succeeding contractions (fig 1). In most cases myotonia seems to disappear, but in a few a definite amount remains in spite of continued contractions. In mild cases motion may be free after two or three contractions, in marked cases progressive improvement may occur for twenty or more contractions. The importance of this characteristic in the diagnosis of myotonia has not been sufficiently realized. Many of the apparent exceptions in the literature are conditions which simulate but are not myotonia. Other apparent exceptions probably fall into the following three groups. 1) Although at times a definite improvement of the myotonia occurs in the first few contractions following rest, the degree of myotonia which persists in spite of repeated contractions may be appreciable. Even those cases in which the myotonia seems to disappear completely might show some degree of residual myotonia if the contractions were recorded with sensitive instruments. It is thus possible to speak of an "initial myotonia" and a "residual myotonia", this assumes that the

same phenomenon is dealt with in both cases, an assumption probably justified but for which proof is yet lacking. A striking example is the unusual case described by Garra and Garra (53) of myotonia limited to the distribution of a single nerve. In this case the first contraction lasted 70 seconds, succeeding contractions decreased in length until the duration was eight seconds, further contractions did not decrease in duration. 2) In severe cases of myotonia repetition of certain movements may be associated with increasing difficulty in execution of the movement almost to the point of rigidity, followed, however, by improvement if the movement is continued. In this group probably belong those cases described as having "paradoxe myotonie" (122, 133), that is, a myotonia which apparently increases with repetition of movement. The explanation in these instances is that the movements involve the contraction not of a single muscle but of several antagonistic muscles. In the case of the fingers, for example, the flexors on contracting the first time do so against relaxed extensors and develop a mild degree of myotonia. Since the extensors must contract against the myotonic flexors, they contract forcefully and develop more marked myotonia. The flexors when they contract again must now overcome the myotonia of the extensors and the movement is thus slow and with marked effort and the myotonia developed is greater. The same is true of the subsequent contraction of the extensor muscles. When the decrease in myotonia resulting from repetition of the movement overcomes the increase in myotonia resulting from increase in strength of contraction, the movements become easier and faster. If the disease is severe and the patient makes a sudden forceful movement, the entire body may become rigid, and the patient, being unable to move, may fall. 3) Although myotonia is generally most severe on the first contraction, it occasionally appears to increase in degree for one or, rarely, two contractions before it begins to improve (106).

The decrease of the myotonia with repetition of contraction is not a fatigue phenomenon since the myotonia is gone long before fatigue sets in and the strength of contraction increases after the myotonia disappears. The decrease of myotonia would appear to be more closely related to those changes which are associated with what is usually called "warming-up."

The corollary to the decrease in myotonia with repetition of the contraction is the increase in myotonia with rest. The condition is usually most severe in the morning. "Stiffness" in the legs is evident only after staying in one position for some time. The more completely the contractions are freed of myotonia by repetition of the contraction, the longer the rest required for the return of the myotonia to its original level.

4 Variations with force of contraction

Within certain limits myotonia increases with increase in force of contraction. Mild degrees of myotonia may not be evident except in acts requiring marked effort. A patient who may be able to open and close his hands with no noticeable difficulty may not be able to release the dynamometer. Above a certain limit, increase in force of contraction does not seem to increase the myotonia. When myotonia has apparently disappeared following weak contractions, it may occur with stronger contractions.

5 Dual nature of myotonic contractions

If the fist is tightly clenched and then an attempt made to open it immediately, 15 seconds may be required to open the hand completely because of the slow relaxation. If, however, the hand is held tightly clenched for 15 seconds, it can be opened rapidly with little or no evidence of myotonia (35, 58, 98, 106). What is even more interesting is that if the hand is held tightly clenched for only, say, seven seconds before beginning relaxation, the relaxation is rapid until the hand is partially open but from that point relaxation is slow and to open completely the hand requires eight more seconds. The total duration of the contraction is thus 15 seconds in each case. On the basis of a study of this phenomenon the author (106) has made the following conclusions: 1) The myotonic contraction consists of two superimposed components, a voluntary contraction of the usual type starting and stopping as desired by will and a persisting contraction setting in at the time of the voluntary contraction and lasting for a definite time, 15 seconds in the foregoing illustration, regardless of the duration of the voluntary component. 2) Both components probably involve the same muscle fibers. 3) Myotonia sets in when the

muscle is contracted but not during voluntary maintenance of the contraction 4) The production of myotonia apparently depends on the occurrence of those changes in the muscle which are associated with the actual contraction or shortening of the muscle

6 Slow phase of contraction

Jensen (69) observed a definite slowness of the phase of contraction in kymograph records of myotonic contractions The author has also recorded this slowness of contraction on kymograph records by using heavy weights (Jensen used a weight of 1.8 kilograms) but feels that caution must be used in evaluating it because strikingly similar curves are sometimes obtained with the use of heavy weights in normal individuals The observation that the slowness of contraction is abnormally accentuated in myotonic individuals by cold (102, 106) and by calcium (106) suggests that it represents a significant finding

7 Decreased strength of second contractions

The second contraction of a myotonic muscle may appear weak if the antagonist of that muscle is also myotonic The first time the muscle contracts it does so against no resistance, but after the antagonist has contracted, the muscle must contract against the resistance of the myotonia now present in the antagonist This probably explains the majority of instances in which a weakness of the second and several succeeding contractions is seen A weakness of the second contraction may also occur when the antagonistic muscle is not myotonic (65, 106) In kymograph records, this weakness is most evident when heavy weights are used, possibly because any weakness which occurs is made more evident and because a greater degree of myotonia is obtained The height of succeeding contractions after the second increases until a height equivalent to or greater than that of the first contraction is attained

8 Effect of psychic factors

Minor degrees of myotonia may be present only when the individual is very excited or frightened Sudden fright may cause a markedly myotonic individual to become completely rigid and fall "as a log" Many of these instances can be explained on the basis of a sudden

increase in myotonia as a result of the greater force of contraction associated with marked emotional stimuli, as fright or anger. That increased force of contraction can result in myotonic contractions after the myotonia has apparently been "worked off" has been pointed out. It is possible that other factors are also involved, such as rate of discharge of nervous stimuli and pouring out of various hormones into the blood stream.

9 Effect of circulatory changes

Bremer and Mage (17) reported that venous congestion decreased the myotonia in a patient, whereas Johnson and Marshall (70) found that both ischemia and congestion caused lengthening of the contraction. Using a method more sensitive and more quantitative the author (106), however, was unable to show that venous congestion produced by placing a blood pressure cuff on the arm at 50 mm of mercury for 5 minutes produced any change in the myotonia. Cutting off the circulation to an extremity by means of a blood pressure cuff for $1\frac{1}{2}$ minutes was also without effect on the myotonia.

10 Effect of temperature

Almost invariably patients say that myotonia is increased in the cold. Milder degrees of myotonia may be noticeable only in the cold and in some families myotonia occurs only under the influence of cold (see below). The author was surprised, therefore, to find on careful investigation of a patient with dystrophia myotonica that the myotonia was definitely decreased at 20°C as compared to 40°C , at 20°C , furthermore, the phase of contraction was prolonged and associated with a feeling of weakness. This surprising result was also obtained by Nylin (102) in a patient with dystrophia myotonica.

The results obtained on so few patients do not refute the general opinion that cold aggravates myotonia, but several points must be noted. First, it is possible that cold may increase "residual myotonia" and still decrease "initial myotonia." Second, questioning of patients makes it quite certain that in the cold they suffer from a fairly marked weakness of the muscles. It is quite possible that much of their complaint in regard to cold arises from this weakness of the muscles rather than from an increase in myotonia. In fact, closer questioning of these

patients usually reveals that it is a "numbness" of their hands rather than the myotonia which causes trouble in the cold. Further observations on this point are necessary. Weakness of antagonists could, of course, produce an apparent increase in myotonia. Third, these findings indicate that although it may be true that cold usually aggravates myotonia, at times other factors may produce a decrease in myotonia with cold.

The manner in which cold affects the muscle needs further investigation. A direct cooling of the muscle suggests itself. Various investigators have shown that the temperature of the muscles is definitely lowered by the external application of cold (8, 92). Since the change in temperature is of appreciable degree to depths of 2 cm and more, it seems probable that many of the muscles are definitely cooled. In paramyotonia, however, in which weakness and at times myotonia occur in the cold it is interesting to note that an effect on the flexors and extensors of the fingers is obtained if the hand is placed in cold water and the forearm kept warm (131). Direct cooling of the muscles in this case can hardly be considered and a reflex vasoconstriction of the vessels in the muscles has been postulated. Against this, in myotonia at least, are the observations described above on the very limited effect of circulatory changes on myotonia.

11 Effect of miscellaneous conditions

Observations indicate that myotonia varies from time to time in a manner not explained by any of the causes previously mentioned. Such variations are in good part due to changes in the various hormones and electrolytes of the body, some of these effects will be described below. Less definite body changes, hormonal or otherwise, which influence myotonia may be described here. Myotonia has been reported to be worse during menstruation (89, 133) and pregnancy (58, 133). Food intake is often stated to improve myotonia, whereas, abstinence from food may aggravate myotonia. Marked fatigue appears to aggravate myotonia. Findley (47) found that myotonia was not affected by hypnosis. Russell and Stedman (117) report that one of their patients noticed that the myotonia was absent for a period of a quarter of an hour to one hour after waking from deep sleep. Hyperventilation has been reported to increase myotonia.

(115), this could not be confirmed by the author. When myotonia is associated with progressive atrophy of the involved muscle, the myotonia decreases as the muscle atrophies. This may be due in part to the marked weakness of the muscle and its inability to contract forcibly enough to produce myotonia. Myotonia is aggravated by acute infections and frequently first becomes evident following a prolonged febrile illness.

12 Effect of drugs on voluntary myotonia

Quinine In 1936 Wolf (151) called attention to the effectiveness of quinine in the treatment of four patients with myotonia, three apparently had myotonia congenita and one dystrophia myotonica. Ten grains of quinine dihydrochloride injected intravenously abolished every myotonic phenomenon within ten minutes, the effect lasting from 15 to 20 hours. Five to ten grains of quinine hydrochloride given by mouth two or three times a day proved to be an effective maintenance dose. Later Kennedy and Wolf (71, 72) reported that as long as quinine was administered it aggravated the muscle weakness in patients with myasthenia gravis and abolished myotonia in patients with myotonia atrophica and myotonia congenita. Doses ranged from 2.5 to 15 grains two to three times a day by mouth. Smith (130), Kolb, Harvey and Whitehill (75), Buckstein (22), Hawke (64) and the author (106) have also reported decrease in myotonia following administration of quinine. Holland and Feld (67) in addition to confirming the effect of quinine in decreasing myotonia observed that the effectiveness of the same dose of quinine appeared to diminish if given on successive days but regained its original effect after a rest period of ten days.

Quinidine has been shown to have an effect similar to quinine (106). Its relative effectiveness as compared to quinine has not yet been determined.

Epinephrine Several authors have recorded the cardiovascular reaction of patients with myotonia to epinephrine, Hauptmann (63), Fünfgeld (50) and Berg (10) found no increased sensitivity to epinephrine in patients with dystrophia myotonica. In a patient with myotonia congenita, Weiss and Kennedy (146) reported that 0.15 mgm of epinephrine produced no increase in blood pressure, but on

the contrary a slight decrease, while the pulse rate did not change. The effect of epinephrine on the myotonia has received less attention. Pansini (quoted from Poncher and Woodward (105)) found that epinephrine made his patient with myotonia congenita definitely worse. Lindsley and Curnen (88), estimating the degree of myotonia by the duration of the associated electrical activity, report that 0.35 cc of a 1:1000 solution of epinephrine hydrochloride given intravenously to a patient with myotonia congenita caused a marked increase in the duration and size of the groups of impulses. The same authors found no effect from epinephrine in a patient with dystrophia myotonica. Kennedy and Wolf (71), dealing with cases of both myotonia congenita and dystrophia myotonica state that epinephrine produced "extreme initial rigidity in myotonia."

By use of a sensitive and quantitative method, the author was able to show that epinephrine definitely decreased the myotonia in each of six patients with dystrophia myotonica in whom the effect was studied (106).

The method deserves a brief description. The forearm and hand are firmly immobilized in a special holder so that only the thumb is free to move. The thumb is connected by a string to the rider of an ergograph. The movements of the rider are recorded on a kymograph. The movements of the thumb are adduction-opposition and abduction-extension. In the patients studied only the muscles producing adduction-opposition exhibited myotonia. A quantitative measure of the degree of myotonia was obtained by having the patient perform four complete contractions and relaxations and totaling the time required for relaxation of each of the first three contractions. Groups of four contractions repeated at approximately ten-minute intervals for as long as two hours show very nearly the same degree of myotonia. To determine the effect of a drug, tests were taken at approximately ten-minute intervals, after two to four tests which served as controls, the drug was administered and the tests continued until the effect of the drug had disappeared or the fatigue of the patients prevented further tests.

After the subcutaneous injection of epinephrine a decrease in myotonia is evident in 5 to 10 minutes, reaches its greatest extent in 15 to 25 minutes and is practically gone in 45 to 60 minutes. After intravenous injection the decrease in myotonia is most evident in 7

to 12 minutes and gone in 25 to 35 minutes. If the myotonia is of light degree, it may be completely abolished. If the myotonia is marked, the improvement is present but not as evident and may be overlooked. If, in a patient with marked myotonia, the degree of myotonia is partially diminished by the use of quinine, the effect of epinephrine is clearly evident as a further decrease in the myotonia.

It has also been shown that the effect of epinephrine is probably directly on the muscles, rather than on the circulation or on the central nervous system (106).

The different experience of other workers cannot be explained but the method of investigation used in the patients studied by the author is least open to criticism. The response of patients with dystrophia myotonica may be different from the response of patients with myotonia congenita. The possibility that an adrenal insufficiency not present in myotonia congenita exists in dystrophia myotonica and that the effect of epinephrine is only evident in presence of such a deficiency and not under normal conditions must not be overlooked.

Insulin Kennedy and Wolf (71) state that one of their patients with myotonia congenita showed definite aggravation of symptoms after the use of insulin. The author (106) found that insulin when given in sufficient amount to produce symptoms of hypoglycemia produced a fairly marked decrease in myotonia. Since the decrease in myotonia was most marked at the time when it is known that the body is pouring out epinephrine to counteract hypoglycemia, it seems most reasonable to assume that the decrease of myotonia was due to mobilization of epinephrine.

Calcium Abrahamson (1) reported improvement of myotonia by the use of thyroid and calcium. Pamboukis (104) reported temporary relief of myotonia in two patients and permanent relief in another by the administration of calcium chloride and acetylsalicylic acid. Lindsley and Curnen (88), using the duration of the associated electrical activity as a gauge of myotonia, found a significant decrease in the duration in a patient with myotonia congenita and a patient with dystrophia myotonica after the intravenous injection of calcium. The decrease in myotonia was evident subjectively as well as objectively. Kennedy and Wolf (71) state that calcium improves myotonia, but it is not clear whether this statement represents their

experience or that of the authors they quote Poncher and Woodward (105) found that calcium decreased the number of attacks in their patient diagnosed as myotonia congenita (See below, however, regarding the diagnosis in this case) Calcium gluconate, given intravenously by the author (106) to three patients with dystrophia myotonica produced a definite improvement in each case The improvement varied in the different patients but was most marked in a patient with a low normal blood calcium and an unequivocal Chvostek sign In the same patient the calcium produced a difficulty in completing the contraction which was most evident at the time when the myotonia was least The nature of the difficulty in contraction is not clear

Thyroid Jensen (69) observed a decrease in the myotonia after the administration of thyroid tablets, in view, however, of the time necessary for thyroid to produce its effect, Jensen's statement that an effect on the myotonia could be determined in one hour after taking two tablets of thyroid casts doubt on the observations Pansini (quoted from Poncher and Woodward (105)) administered thyroid to one of his patients with questionable success Brock and Kay (19) observed no improvement from 9 grams of thyroid a day in a patient said to have myotonia congenita but who probably had dystrophia myotonica (baldness, testicular atrophy, cataracts at 48 years in father) Weiss and Kennedy (146) reported that thyroid substance and thyroxin in large doses produced no signs of hyperthyroidism but seemed to aggravate the condition of a patient with myotonia congenita Keschner and Finesilver (73) noted no benefit whatever from treating a patient with dystrophia myotonica with thyroid over a prolonged period Condorelli (29) observed a high tolerance to thyroid in his patient Berkman (11) reported that a patient with myotonic dystrophy who developed hyperthyroidism had less myotonia after thyroidectomy Poncher and Woodward (105) recorded marked improvement with thyroid medication in a child said to have myotonia congenita Some question as to the diagnosis exists (see below) In an adult patient with myotonia congenita the same workers found an accentuation of the myotonia following thyroid administration Kennedy and Wolf (71) state that thyroid improves myotonia but it is not clear that this represents new observa-

tions Milhorat and Wolff (96) reported that thyroid administration did not improve the myotonia in a patient with dystrophia myotonica and that the difficulty might have been increased. One of the author's patients took 5 to 10 grains of thyroid for a period of over two years and did not believe that his myotonia was affected, although other benefits were evident.

Ephedrine Comroe (28) reported improvement in a patient with myotonia congenita with the use of ephedrine sulfate. Kennedy and Wolf (71) state that ephedrine exaggerates myotonia. The author (106) observed no effect from ephedrine even when given intravenously.

Pilocarpine Hauptmann (63) and Fünfgeld (50) noted exaggerated general reactions to a test dose of pilocarpine in patients with dystrophia myotonica. Adie and Greenfield (2), however, thought the susceptibility to pilocarpine was decreased rather than increased in one of their patients. Weiss and Kennedy (146) also noted no increased sensitivity to pilocarpine. Monrad-Krohn (98) found that 0.0075 gram of pilocarpine given intravenously caused a marked diminution of myotonia. Pamboukis (104) and Lindsley and Curnen (88) reported that pilocarpine produced an increase in myotonia in their patients. Pilocarpine failed to produce an appreciable change in the myotonia of one of the author's patients in spite of other marked reactions (flushing, salivation and abdominal cramps) (106).

Prostigmin Russell and Stedman (117) in 1936 reported that in a case of myotonia congenita and in a case of myotonia atrophica the injection of 1.25 mgm of prostigmin made the myotonia definitely worse. Kennedy and Wolf (71, 72) and Kolb, Harvey, and Whitehill (75) also found that prostigmin aggravated myotonia. Kolb, Harvey and Whitehill showed further that if the prostigmin were given simultaneously with quinine it directly antagonized the full therapeutic effect of quinine. Evert (45) noted improvement in patients with myotonia, and Buchstein (22) states that prostigmin did not increase the strength or alter the myotonia in a patient with dystrophia myotonica.

Acetylcholine and acetyl-beta methylcholine Lanari (86) found that the intra arterial injection of 0.04 gram of acetylcholine, which in normal individuals produces no motor effect, provoked in myotonic

patients a reversible muscular contracture in the injected extremity. An injection into the brachial arterial at the elbow produced, in succession, flexion of the fingers with extension of the hand, slight flexion of the forearm on the arm, flexion of the hand, and finally pronation of the hand. The movements were slow and continuous and lasted approximately a half minute. They occurred in every one of the six patients with myotonia. After the immediate effects had passed the patients did not observe any change in the myotonia. Kolb, Harvey, and Whitehill (75) state that "clinically acetylcholine, acetyl-beta-methylcholine and carbinianocholine when tried by us and others have had no effect in myasthenia gravis or on myotonus." Acetylcholine and mecholyl (acetyl-beta-methylcholine) given subcutaneously did not affect the myotonia in the author's patients (106).

A marked muscular effect following subcutaneous injection would be unlikely because of the rapid destruction of the drug. The actions of acetylcholine have been divided into the muscarine-like action and the nicotine-like action. It is the nicotine-like action which is responsible for the effect of acetylcholine on skeletal muscle (34). Acetyl-beta-methylcholine has practically no nicotine-like actions and would not be expected to produce an effect on myotonia unless it did so as a result of its muscarine-like or parasympathomimetic action (6).

Atropine Hauptmann (63) in one case of dystrophia myotonica and Funfgeld (50) in two cases of dystrophia myotonica found no evidence of excessive general reaction to atropine, neither notes any effect on the myotonia. Erb (41), Bremer and Mage (17), and Keschner and Finesilver (73) state that atropine had no evident effect on myotonia. Weiss and Kennedy (146) observed a marked improvement in the myotonia following administration of atropine. This effect of atropine was greatly enhanced by thyroidization of the patient. Pamboukis (104) also noted improvement in myotonia with atropine. Kennedy and Wolf (71) list atropine as producing questionable improvement of myotonia and tincture of belladonna as producing questionable exaggeration. In one patient the author observed no definite effect following the intravenous injection of

0.5 gr of atropine (106)

reported that benzedrine decreased the

drowsiness of a patient with dystrophia myotonica and produced a feeling of well being but mentions no effect on the myotonia. In one of the author's patients the oral administration of 40 mgm produced no definite effect on the myotonia in 70 minutes.

Ergotamine Lindsley and Curnen (88) report that ergotamine tartrate (0.25 mgm intravenously) did not affect the duration of the myotonia. In one of the author's patients 1 mgm subcutaneously did not produce an appreciable effect in 50 minutes.

Alcohol Improvement following the ingestion of alcohol has been reported by many authors. It was observed by Blumenau (quoted from Erb (42)), Erb (42), Deleage (37), and recently reported again by Russell and Stedman (117), and Kennedy and Wolf (72).

Hyoscine The observation by Bremer and Mage (17) that hyoscine did not affect the myotonia in their patient agrees with the author's observation in two patients (106).

Caffeine The intravenous administration of $3\frac{1}{2}$ and $7\frac{1}{2}$ grains of caffeine to one of the author's patients did not affect the myotonia (106).

Glycocoll Slauck (129) states that glycocoll plus testicular hormone benefited patients with dystrophia myotonica but does not state whether the benefit included decrease in myotonia. Lindsley and Curnen (88) observed no change in the myotonia in patients with dystrophia myotonica who took glycocoll. Three of the author's patients received glycocoll over a period of many months without showing any appreciable change in the myotonia as judged by gross examination.

Creatine Poncher and Woodward (105) found that creatine ingestion aggravated the myotonia in an infant with myotonia congenita (see below) and in an adult with myotonia congenita. Creatine administration, however, did not affect the myotonia of a patient with dystrophia myotonica and a patient with myotonia congenita studied by Milhorat and Wolff (97).

Potassium Russell and Stedman (117) state that the administration of 5 grams of potassium chloride in solution by mouth produced a striking increase of the myotonia in a patient with myotonia congenita. A similar but less striking effect was produced in a patient

with dystrophia myotonica Kennedy and Wolf (72) confirmed this observation Kolb, Harvey and Whitehill (75) state that potassium chloride did not affect the myotonia in their patients.

The following observations suggest that the further investigation of the relation of potassium metabolism to myotonia will yield valuable information 1) Glucose by mouth lowers the potassium level in the blood serum (3, 26), many patients with myotonia state that a good meal appears to decrease the myotonia 2) Adrenalin lowers the serum potassium (3, 26), adrenalin decreases myotonia 3) Insulin lowers serum potassium (3), insulin decreases myotonia (it should be noted, however, that the insulin effect on myotonia appears to be due to adrenalin liberation, whereas, the effect on serum potassium will occur even if a drop in blood sugar is prevented by glucose) 4) Potassium by mouth increases serum potassium, potassium by mouth has been stated to increase myotonia

Parathyroid Brock and Kay (19) observed no effect on the myotonia in a patient with dystrophia myotonica while giving parathyroid gland simultaneously with thyroid and potassium iodide Rouqués (115) observed no change in the myotonia in dystrophia myotonica from the use of Collip parathyrine and considered treatment with this extract dangerous Lindsley and Curnen (88) state that attempts to increase the calcium content of the blood by means of injection of parathyroid extract (Lilly) did not succeed in raising the calcium content of the blood sufficiently to change the myotonia Kennedy and Wolf (71) list parathyroid as producing improvement in myotonia but probably base this on the work of others Kolb, Harvey and Whitehill (75) observed no clinical change in the myotonia from injections of parathormone intramuscularly (Lilly) in doses that produced a definite change in the blood calcium and phosphorus Poncher and Woodward (105) gave parathyroid extract to their patient with no benefit

Anterior pituitary extract Kennedy and Wolf (71) list anterior pituitary extract as producing questionable exaggeration of myotonia No objective change in the myotonia was observed in one of the author's patients who received fairly large doses of Anterior Pituitary Extract (Squibb) over a period of months Another patient believed that the myotonia was definitely less

Testicular extract Jensen (69) reported improvement in myotonia

following injections of orchitic substance Slauck (129) treated patients with glycooll and testicular extract with improvement but does not mention any effect on the myotonia Waring, Ravin and Walker (145) observed no effect on myotonia from the injection of large doses of testosterone propionate in three patients

Pamboukis (104) used *aspirin* along with calcium and obtained improvement in myotonia Kolb, Harvey and Whitehill (75) reported no change after the use of *adrenal cortex* Pamboukis (103) reported beneficial results after forty injections of a solution of *posterior pituitary* Erb (41) thought that *strychnine* increased myotonia slightly Johnson and Marshall (70) obtained some improvement from strychnine Frink (quoted from Kennedy and Wolf (71)) states that myotonia was improved following tablets of *thymus gland* by mouth Bremer (15) found that intramuscular injection of a 1 per cent *novocaine* solution did not affect myotonia but did affect hypertonus of the type found in tetanus and Parkinsonian rigidity *Physostigmine salicylate* is listed by Kennedy and Wolf (71) as producing slight exaggeration of myotonia Kennedy and Wolf (71) list *veratrine* as producing a questionable exaggeration of myotonia and *viosterol* as producing improvement *Ketosis* produced by diet did not affect the myotonia in a patient with myotonia congenita studied by Milhorat and Wolff (97)

Kolb (74) studied what appears to be a congenital myotonia occurring in goats In these animals quinine and other cinchona derivatives, with the exception of quitenins, quitenidine, eucupine and atebnin relieved the myotonic state Prostigmin and pilocarpine aggravated the symptom and prostigmin reversed the previously beneficial effect of quinine. There was some suggestion that ephedrine and barium increased the myotonia Atropine, adrenalin, potassium, calcium, magnesium, guanidine and alcohol failed to modify the myotonia.

MYOTONIA ASSOCIATED WITH CONTRACTIONS PRODUCED BY MECHANICAL STIMULI (MECHANICAL MYOTONIA)

Mechanical irritability of myotonic muscles

A normal muscle may be made to contract by a mechanical stimulus such as a blow with a percussion hammer The ease with which the muscles of the body may be stimulated to contract will depend in

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MYOTONIA ASSOCIATED WITH CONTRACTIONS PRODUCED BY MECHANICAL STIMULI (MECHANICAL MYOTONIA)

Mechanical irritability of myotonic muscles

A normal muscle may be made to contract by a mechanical stimulus such as a blow with a percussion hammer The ease with which the muscles of the body may be stimulated to contract will depend in

great part upon their inherent irritability. Myotonic muscles usually show an increased irritability to mechanical stimuli. The accessibility of a muscle and its tension are also important factors in its response to mechanical stimulation. The accessibility of the muscle to stimulation is determined by its location, superficial or deep, and the amount of fat in the subcutaneous tissues. Stretching a muscle, and thus increasing its initial tension, increases the irritability of a muscle (149). A contraction can thus be obtained by percussion of a stretched muscle when it cannot be obtained from a relaxed muscle.

Myotonic phenomena

The contraction and relaxation of a normal muscle following mechanical stimulation is rapid, the entire event usually taking less than a second, although in highly developed muscles it may last somewhat longer. The contraction and especially the relaxation of a myotonic muscle following mechanical stimulation are prolonged. If a large muscle, such as the deltoid, is stimulated, usually only the fibers struck contract and a furrow or a dimple is formed. Small muscles may contract as a whole. In the case of some muscles, as the chin muscles, contraction necessarily produces an elevation. In those instances where a furrow or a dimple forms, the slowness of the contraction is not as evident as is the persistence of the furrow or dimple, which may be for more than 30 seconds. The small muscles of the thenar eminence contract as a whole, and here the slow contraction as well as the abnormally slow relaxation are clearly seen.

It is frequently found that many muscles which show no voluntary myotonia show mechanical myotonia. The converse has also been claimed to occur but this must be questioned. In sibships showing dystrophia myotonica, examination of apparently unaffected individuals will sometimes show the presence of mechanical myotonia when voluntary myotonia has not yet developed. In some patients in whom the voluntary myotonia has improved for unknown reasons, the mechanical myotonia has persisted.

As in the case of myotonia associated with voluntary contractions, the prolongation of the contraction produced by mechanical stimulation decreases with repetition of the contraction (102, 133). A number of attempts to determine decrease in mechanical myotonia pro-

duced by repeated voluntary contractions gave inconclusive results. Mechanical myotonia varies from day to day and with different bodily states, the factors involved have not been determined. Bürger and Schellong (23) report a prolongation of mechanical myotonia by cold, but Nylin (102) reports that marked cold reduces the mechanical irritability so markedly that no reaction can be obtained. Decrease of mechanical myotonia has been reported following intravenous injection of calcium (88) and intravenous injection of quinine (71).

The relation of the so-called "*idiomuscular contraction*" to myotonia is of interest. When the muscles of some individuals are stimulated mechanically, the fibers contract and relax with normal rapidity but during the contraction of these fibers or immediately afterwards an elevation forms in the fibers at the point of stimulation. The height which the elevation attains depends on the intensity of the stimulation and the susceptibility of the muscle to production of the phenomenon. It is most likely to be seen in the pectoral muscles of patients suffering from chronic illnesses associated with emaciation (30). The elevation forms rapidly, subsides gradually and disappears within three to ten seconds. With sufficiently strong stimulation this idiomuscular contraction may be produced in many normal individuals, so that it is necessary to distinguish it from mechanical myotonia. This is easily done if it is remembered that in myotonia a furrow or dimple forms as a result of the persistence of the contraction of the stimulated muscle fibers. In the idiomuscular contraction the stimulated muscle fibers can be seen to contract and relax normally and at the same time or immediately afterwards an elevation forms at the point of stimulation. Idiomuscular contractions are sometimes seen in myotonic individuals, usually in muscles which do not show myotonia on mechanical stimulation. Curschmann (32) thought that the tendency to formation of idiomuscular contractions was decreased in myotonia.

MYOTONIA ASSOCIATED WITH CONTRACTIONS PRODUCED BY ELECTRICAL STIMULI (ELECTRICAL MYOTONIA)

Erb's (41) description of the reactions of the nerves and muscles of myotonic patients to electrical stimuli has undergone only minor modifications and a summary of his clear description serves as an

excellent background for understanding these reactions. The reaction of the muscles to mechanical and electrical stimulation he called the "myotonic reaction." Changes to electrical stimulation consisted of changes in irritability, that is, in the strength of current required to produce a contraction, and changes in type of response.

Nerves The motor nerves showed normal irritability to *faradic* currents. Contractions produced by very weak currents showed no myotonia. Stronger currents produced myotonic contractions in which the duration increased with increase in strength of current. Single induction shocks did not produce myotonic contractions. The *galvanic* irritability of the motor nerves was also quantitatively normal. ACC was often equal to or greater than CCC. Contractions were always normal in character, that is, showed no myotonia.

Muscles The irritability of the muscles to *faradic* stimulation was normal or somewhat increased. Again a certain strength of current was necessary before the contractions produced showed myotonia and the degree of myotonia increased with increase in strength of current. Contractions produced by single induction shocks did not show myotonia. The *galvanic* irritability of the muscle was quantitatively normal or increased. ACC was often equal to or greater than CCC. Normal contraction could not usually be obtained, especially with the anode, even with weak currents, only slow tonic contractions, persisting during the flow of the current occurred. Such contractions are obtained normally only with very strong currents (closing tetanus). In these cases, of course, no opening contractions were obtained. With weak currents the contraction stopped when the current was stopped, with stronger currents the contraction persisted for a varying time after the opening of the current.

Kramer and Selling (82) found in their careful study of the electrical reactions in myotonia that the myotonic contraction following galvanic stimulation is more clearly seen if the muscle is stimulated at a distance from the motor point probably because in the region of the motor point stimulation of nerve instead of muscle is obtained. Also, the difference in irritability between the motor point of the muscle and other parts of the muscle was less than normal. By recording the contractions and using rapidly repeated stimuli, Jensen (69) showed that the contractions obtained by single induction shocks of the nerve or muscle show a small amount of myotonia. It had been

overlooked because of its small degree, which is probably a result of the weakness of the contraction obtained from single induction shocks

Various other special types of reactions have been described Steinert and Passler (quoted by Curschmann (32)) found that frequently no myotonic contraction follows short galvanic or faradic stimulation, but if the stimulus is prolonged and the strength remains the same, a myotonic contraction occurs Erb's "double contraction" (102), obtained on galvanic stimulation of the muscle with strong currents, is a quick contraction followed by a more prolonged contraction This is most clearly seen when the muscle is stimulated at the motor point (82) and probably depends upon stimulation of both nerve and muscle (81) Erb's (41) "wave phenomenon" is best seen when the stimulating electrode is placed not directly on the muscle but at the end of the tendon With a galvanic current of sufficient strength, a tonic contraction is first produced which changes into a restless, undulating motion of the muscle Contraction waves, following each other at about one second to three second intervals, move through the body of the muscle, the movement is toward the electrode, if it is the anode, and away from it, if it is the cathode

As in the case of mechanical myotonia, electrical myotonia is usually more widespread than voluntary myotonia and probably can be found before voluntary myotonia makes its appearance The duration of the myotonia decreases with repetition of the contractions produced by both faradic and galvanic currents (12, 31, 38, 69, 82, 102) Delprat (38) states that electrical myotonia is decreased by preceding voluntary contractions Mild degrees of cold are said to increase the myotonic reaction (123) but marked cold decreases the electrical irritability almost to extinction (102) When atrophy is associated with the myotonia, the excitability of the muscle is usually diminished and stronger currents are necessary for production of the reactions Kennedy and Wolf (71) report that the myotonic reaction to mechanical and galvanic stimulation was unchanged after spinal anesthesia and was abolished by quinine intravenously

BLOOD CONSTITUENTS AND METABOLISM IN DISEASES ASSOCIATED WITH MYOTONIA

Many studies have been made on the composition of the blood and the metabolism in patients with myotonia In general the results

have been normal and when abnormal their relation to myotonia has been questionable. Blood calcium determinations both in patients with myotonia congenita and patients with dystrophia myotonica have been normal in almost all cases, rarely, they have been low. The cholinesterase of the blood has been studied (95, 117, 134) in several cases with varying results which permit no interpretation, especially in view of the general difficulty at present of interpreting cholinesterase values. Blood bromide (4), blood iodine (4), blood sodium (60), blood potassium (60) have been reported as normal in patients with dystrophia myotonica. Alkaline reserve has been reported (4) as high normal or slightly increased. The basal metabolic rate is lowered in dystrophia myotonica but the myotonia is not improved by administration of thyroid. Creatine metabolism has been studied in myotonia congenita and in dystrophia myotonica by many workers (47, 75, 96, 99, 105, 111, 129) but no relation between myotonia and creatine metabolism has been definitely shown except where hypothyroidism is also present (105).

PATHOLOGICAL CHANGES IN MYOTONIC MUSCLES

Erb (41) considered the pathological changes in myotonic muscles to consist mainly of an enormous hypertrophy of the fibers and a great increase in sarcolemma nuclei, in addition, an indistinctness of the transverse striations, some vacuole formation, and a slight increase of the interstitial connective tissue were also frequent. Jacoby (68) found that if the muscle were fixed while it was extended, it appeared more normal and he felt that most of the findings considered characteristic of myotonia were artifacts resulting from the marked tendency of the muscle fibers to contract after removal from the body. Slauck (128) also reported that the hypertrophy was not very marked and the increase in sarcolemma nuclei was slight. He found the variation in size of the fibers to be striking at times. Comroe (28) found increase in size of the muscle fibers and an indistinctness of the cross-striation but no increase in the sarcolemma nuclei.

Where myotonia is associated with atrophy, as in dystrophia myotonica, marked and rather characteristic changes are evident in the muscles. These need not be described here, a good description can be found in the article by Adie and Greenfield (2).

LOCATION OF THE DEFECT IN MYOTONIA

Much discussion has arisen from the question of whether myotonia is the result of a change in the muscles (myogenic) or in the nervous system (neurogenic). Efforts to settle this question have in great part centered around attempts to determine whether the prolonged contraction is associated with action currents. A nervous stimulus causes the muscle fiber as a whole to contract and produces a wave of electrical change (action current) which travels throughout the length of the muscle fiber. A muscle stimulated at such frequent intervals that it remains in a persistent state of contraction is said to be in tetanus. If the electromyogram should show evidence of action currents during myotonia, there is some basis for assuming that the contraction is produced by repeated nerve impulses, this may be taken as evidence for a neurogenic origin of myotonia. If action currents are absent, myotonia is probably a contracture. A contracture is a sustained contraction in which, in contrast to tetanus, action currents are absent and the contraction is not propagated through the muscle fiber (54). A contracture is the result of a change in the muscle and the mechanical change or shortening persists for an abnormally long time after the stimulus producing the contracture has ceased. A contracture although not associated with action currents may be accompanied by a slow change in potential without oscillations indicating action currents. Schäffer (121), Adie and Greenfield (2), Condorelli (29), Luisada (90), and Mikamo and Hisajoshi (94) reported the absence of action currents during the prolonged myotonic contraction and believed that myotonia had its origin in the muscle. In addition Condorelli (29), Mikamo and Hisajoshi (94), and Luisada (90) found the contractions to be associated with the slow potential change considered characteristic of contractures.

On the other hand Gildemeister (56) found action currents in myotonia following voluntary contractions, Gregor and Shilder (57) found action currents in voluntary myotonic contractions and myotonic contractions produced by faradic stimulation but failed to find action currents associated with mechanical myotonia or myotonia following galvanic stimulation, Bürger and Schellong (23) found action currents associated with mechanical myotonia, and Lindsley and Curnen (88) found action currents in voluntary and mechanical myotonia.

Gregor and Shilder, and Lindsley and Curnen believed that myotonia was neurogenic and of reflex origin. Lindsley and Curnen believed that it was due to the persistent discharge of hyperexcitable sensory end-organs in the muscle, a proprioceptive reflex. The possibility of an "imbalance of the mechanism of reciprocal innervation whereby inhibitory processes are insufficient to abolish residual excitatory ones" was also suggested by Lindsley and Curnen but rejected as unlikely.

Attempts to distinguish a tetanus from a contracture by the presence or absence of action currents, however, are beset with many difficulties. On the one hand, if no oscillations are found the objection may be made that the instrument used to record electrical variations was not sufficiently sensitive or responsive. Hoffmann (66) found oscillations in the classical veratrine contracture and believed the contraction was a tetanus and that the workers who had failed to find action currents had not used sufficiently sensitive instruments. On the other hand, if action currents are found they may be considered as resulting from fibrillary twitchings superimposed upon a contracture. Such fibrillary twitchings are frequently seen in acetylcholine and veratrine contractures. Schaffer (120) found action currents associated with Tiegel's contracture in man. The presence of action currents does not, therefore, appear to rule out a contracture. The action currents found by Lindsley and Curnen (88) may well be produced by a proprioceptive reflex and yet may not be the cause of the myotonia. The sudden catch which frequently occurs during relaxation (fig 1), appears to result from the dual nature of the myotonic contraction. The catch may, however, by stretching the muscle, result in a reflex stimulation and contraction of some of the muscle fibers.

Several workers have performed experiments which apparently exclude a central origin for myotonia. Grund (59) reported that the myotonic reaction persisted in limbs paralyzed by intrathecal injection of stovaine, so that all spontaneous and reflex activity was absent. Schaffer (121) showed that myotonia persisted when the nerve endings in the muscles were paralyzed by regional anesthesia. Kennedy and Wolf (71) found that mechanical and electrical myotonia persisted following spinal anesthesia and that the effect of quinine in inhibiting myotonia was present after spinal anesthesia. These experiments

furnish proof that the location of the disturbance producing myotonia is peripheral, in the muscle or in the neuromuscular junction

Bürger and Schellong (23) from their experiments and Büsow (24) on the basis of Grund's (59) and Schäffer's (121) experiments decided that although the contraction was a tetanus it was due to a change in the muscle. They give no clear explanation of how this might occur but in this connection the character of the contraction of a glycerin poisoned muscle might be mentioned. Sollman (132) states "The muscles poisoned with glycerin respond to single stimuli by prolonged contraction, the curve having a superficial resemblance to that of veratrine, but being rather more irregular. The glycerin contraction is, however, a true tetanus, due to greater irritability of the muscle substance, the action current of each contraction sufficing to start another contraction." A tetanus might thus have a peripheral origin.

Strong evidence in favor of a peripheral defect involving the muscle itself rather than the neuromuscular junctions is obtained by comparing the characteristics of myotonia to those of contractures (106). A brief description of a group of closely related though diversely produced contractures and a comparison of their characteristics with those of myotonia will serve to show the relationship. The contractures to be described are veratrine contracture, Tiegel's contracture, neuromuscular contracture and acetylcholine contracture.

If a strip of frog's muscle is immersed in a veratrine solution, stimulation no longer produces a rapid contraction and relaxation but results in a rapid contraction followed by a slow relaxation, the so-called veratrine contracture. In some very irritable muscles a similar slow relaxation may be seen on strong electrical stimulation of the muscle in the absence of veratrine. This prolonged contraction is known as Tiegel's contracture, it is commonly seen in the laboratory on repeated stimulation of highly irritable frog's muscles. Kruse (84) has shown that the same type of prolonged contraction obtained by a very strong stimulus could be produced by a stimulus of moderate intensity following veratrine and it seems justifiable to conclude with Gasser (54) that veratrine only reveals a fundamental characteristic of skeletal muscle.

Tiegel's contracture has also been shown to be present in man by

Mosso (100) and by Schaffer (120) On direct stimulation of the flexor muscles in the forearm by strong galvanic or faradic currents at two-second intervals, the slowness of relaxation becomes evident in a few contractions, reaches a maximum after several contractions and then gradually disappears Schäffer (120) found that individuals varied markedly in the degree to which they showed this contracture and thought it possible that those who showed it in a high degree bordered on the pathological Since the contracture occurs even when the brachial plexus is blocked by novocaine (120), reflex production of the contracture is ruled out

Most attempts to produce contractures by stimulation of the nerve have been unsuccessful but Bremer (16) has shown that a contracture can be produced in frog's muscle quite regularly by suitably spaced electrical stimuli to the nerve Such neuromuscular contractures are most easily produced in those muscles which show Tiegel's contracture

Acetylcholine in adequate concentration produces a contracture in many of the muscles of a frog but not in normal mammalian muscle If the nerve to the muscle is permitted to degenerate, mammalian muscle shows a response to acetylcholine similar to that of frog's muscle Those amphibian muscles which show the greatest sensitivity to acetylcholine exhibit the most marked Tiegel's contractures (142) It seems probable that the same fundamental tendency to contracture is involved in these instances

It is seen from the above that a tendency to reaction by contracture exists in the muscle This "contracture reaction tendency" varies in different animals and in different muscles of the same animal It is augmented by veratrine and by denervation It may be brought out by electrical stimulation of the muscle (Tiegel's contracture), by electrical stimulation of the nerve (neuromuscular contracture), or by acetylcholine

It is evident that myotonia following voluntary contraction is comparable to neuromuscular contracture Their identity has been advanced by Bremer (16, 17) Myotonia following electrical stimulation is comparable to Tiegel's contracture, especially as described in man by Mosso (100) and by Schaffer (120) This similarity of the myotonic reaction and Tiegel's contracture in man, pointed out by Schaffer (119), is so marked that it is difficult to avoid the conclusion

that they are different degrees of the same phenomenon. The similarity of myotonia to the contractures described will be evident on comparison of their reaction to different drugs and conditions.

Possibly the most striking similarity is what has been called the "fatigability" of the contractures, that is, in a succession of contractions, the contracture decreases and soon leaves. After a rest the contracture returns. The "fatigue" of the contracture, however, occurs long before the muscle fatigues. Myotonia, Tiegel's contracture in frogs (54) and in man (120), veratrine contracture (54), and neuromuscular contracture (16), show this fatigability. It is not obvious in acetylcholine contractures.

Epinephrine inhibits Tiegel's contracture in man (120). Epinephrine injected immediately before or simultaneously with acetylcholine inhibits or totally prevents the production of acetylcholine contracture in denervated mammalian muscle (55). The effect of epinephrine on voluntary myotonia has been noted above. Epinephrine has not been shown to have any effect on veratrine contracture or neuromuscular contracture (14).

Quinine suppresses veratrine contracture (62), neuromuscular contracture (18), acetylcholine contracture in denervated mammalian muscle (62), and myotonia.

Atropine decreases the height of Tiegel's contracture (120, 142), neuromuscular contracture (14), acetylcholine contracture (20, 33, 109), and veratrine contracture (110). The effect of atropine on myotonia has been slight in most cases but in one patient (146) it markedly decreased the myotonia. The lack of effect usually observed may well be correlated with the large doses required to show an effect in the case of most of the contractures.

Calcium decreases veratrine contracture (85), acetylcholine contracture (54), and myotonia.

Eserine increases acetylcholine contracture (20, 33), facilitates the production of neuromuscular contracture (46) and increases Tiegel's contracture in man (120). Prostigmin, chemically related to eserine and having a similar action, aggravates myotonia.

Alcohol decreases myotonia and also inhibits veratrine contracture (v. Fray—quoted by Schüller and Athmer (124)).

Lanari's results (86) described above suggest an increased sensitivity

to acetylcholine and an increased tendency to contracture reaction of myotonic muscles

It is evident that the properties of myotonia are largely those of the group of contractures which have been described. If myotonia is considered to be a contracture, it would follow that the defect is partially or entirely in the muscles.

Additional insight into the location of the defect in myotonia and the status of the neuromuscular transmission is obtained by analyzing that characteristic of myotonia which has been described as "the dual nature of the myotonic contraction." Since the duration of the myotonia is not affected by the duration of an associated tetanic contraction (see above), the stimuli which maintain tetanic contraction must not affect the myotonia. Myotonia sets in only when the muscle contracts and not during maintenance of the contraction, the nerve impulses produce myotonia when they cause contraction of the muscle but not when they maintain contraction. This observation combined with the known effectiveness of stimuli other than nerve impulses (mechanical and electrical stimuli) in producing myotonia makes it reasonable to conclude that the manifestation of myotonia is more dependent on the changes associated with actual contraction than on the nature of the stimulus producing the contraction. This means, of course, that the defect is in the muscle. A defect in neuromuscular transmission could play only a minor accessory part in production of myotonia.

Analyzing the dual nature of the myotonic contraction from a different viewpoint, it can be shown that myotonia cannot be explained as resulting from an abnormality of the neuromuscular transmission alone. Let us assume that the muscle is normal in myotonia and that myotonia is due to an abnormality of the neuromuscular transmission resulting in a prolonged stimulation of the muscle. In terms of the chemical hypothesis of neuromuscular transmission, such a prolonged stimulation would mean an excessive liberation of acetylcholine by the nerve impulse or a deficient action of cholinesterase or both. Under such circumstances, the longer the duration of tetanus, the longer would be liberation of acetylcholine and the more marked the resulting myotonia. This, of course, does not agree with the observations. If, moreover, a muscular defect is assumed to be the main cause

of the myotonia, the occurrence of a defect in neuromuscular transmission of the above described type as an additional factor is unlikely. From the observation that the stimuli which maintain tetanic contraction do not affect myotonia, a neuromuscular defect would be expected to affect the tetanic contractions rather than the myotonia. Although more careful study of the tetanic contractions is necessary, they appear to be of normal character.

The existence of an increased sensitivity of the muscle to acetylcholine is suggested by Lanari's observation on the effect of intravenously injected acetylcholine in patients with myotonia. A normal stimulus, one in which the acetylcholine liberated was normal in amount and normally destroyed, would be relatively excessive to a sensitive muscle fiber, but the muscle fiber, according to the "all or nothing principle," should respond no differently than it would to a stimulus which was merely adequate. An increased sensitivity of the muscle fiber to acetylcholine cannot in itself cause myotonia and is of importance only when considered in association with the abnormal tendency of the muscle fiber to respond with myotonia.

Because of the contrast which myotonia shows to myasthenia, both in clinical features and in the responses to various drugs, Harvey (61) believes that myotonia is due to an abnormality of neuromuscular transmission, "the threshold of the end plates being lower, or the transmitter of excitation from the nerve endings being more slowly destroyed, than in the normal muscle." The following evidence is given in support of this hypothesis: 1) quinine, which has a curare like action in decreasing the excitability of the end plates (62), alleviates myotonia, (2) prostigmin, which inhibits cholinesterase and therefore the destruction of acetylcholine, aggravates myotonia, 3) potassium ions, which lower the threshold at the motor end plates, aggravate myotonia. Objections to the explanation of myotonia on the basis of increased sensitivity of the muscle fiber to acetylcholine or delayed destruction of acetylcholine have been given. It has, moreover, been pointed out (106) that the action of the drugs may be interpreted in a different manner. Eserine appears from the work of Fung and Shen (46) to have an action on the muscle which may be interpreted as increasing the contracture reaction tendency of the muscle. A similar action of prostigmin would account for its effect on myotonia.

Doubt is cast on the importance of the curare-like action of quinine in myotonia by the observation that epinephrine, which also alleviates myotonia, has a decurarizing action similar to that of potassium ions (112). On the other hand both quinine and epinephrine inhibit the contracture reaction of denervated mammalian muscle to acetylcholine and potentiate the response of skeletal muscle to single maximal induction shocks (62, 25). Quinine, in addition, increases the refractory period of skeletal muscle (62). It is evident that the drug actions furnish no basis for assuming a neuromuscular defect in myotonia.

It may be concluded that the defect in myotonia is mainly or entirely in the muscles and that a defect of neuromuscular transmission could not adequately explain the observed phenomena and is probably not present.

RELATION OF THE ENDOCRINE GLANDS TO MYOTONIA

A disturbance in one or more of the endocrine glands has been suggested as the cause of the change in the muscles. Probably because of the superficial resemblance between tetany and myotonia, the parathyroids most frequently have been thought to be at fault. That this resemblance is only of the most superficial type was pointed out by Erb (41). In contrast to tetany which is frequently painful, occurs spontaneously, is localized mainly in the extremities in the same pattern, and is produced by pressure on the nerve trunk or vessel, myotonia is not painful, occurs always in connection with certain voluntary movements, has the form and localization of the movement made, and cannot be produced by pressure on the nerve trunk or large vessels. In tetany the mechanical, faradic and galvanic irritability of the nerves are definitely increased, in myotonia they are normal or even decreased. In tetany the mechanical and electrical irritability of the muscle are not increased and the contractions are always short, rapid, and without after duration, in myotonia the irritability of the muscles is increased and the contractions are myotonic. Blood calcium determinations in myotonia have usually been normal and parathyroid hormone has not been shown to affect myotonia. It is readily evident that if myotonia has any relation to the parathyroids, the evidence rests on an unfounded belief in the similarity of tetany and

myotonia and possibly on the fact that calcium does, at least at times, decrease myotonia. It may be said that good evidence is lacking that myotonia is due to an abnormality of the function of the parathyroids.

It will be shown that hypothyroidism is associated in some individuals with myotonia. On the other hand most patients with myotonia congenita do not show evidence of thyroid dysfunction. If patients with dystrophia myotonica show thyroid dysfunction it must be connected with their other dystrophic symptoms and not with the myotonia. Thyroid medication has not been effective in myotonia congenita or dystrophia myotonica.

The several cases which have been reported in which the myotonia was worse during menstrual periods and during pregnancy suggest some effect of the gonadal hormones on myotonia but nothing which exclusively implicates the gonads. The effect of adrenalin shows that the adrenals may affect myotonia but evidences of adrenal insufficiency are not usually present and cortical extract is without influence. The pituitary, whose manifold functions are bewildering, may possibly influence myotonia but no well known function can be associated with the muscle change and no good reason exists for postulating such a function. Insulin probably affects myotonia through mobilization of adrenalin.

The relation of the endocrine glands to myotonia may be summarized by the statement that although good evidence exists for believing that myotonia is definitely influenced by the endocrine glands, evidence that the myotonic change in the muscle is produced by any one of the endocrine glands is lacking. To suggest a polyglandular cause clarifies nothing and has no greater evidence in its favor.

RELATION OF THE AUTONOMIC NERVOUS SYSTEM TO MYOTONIA

Mainly because evidences of midbrain involvement have been found in a few patients with dystrophia myotonica, this malady has been ascribed by some to a lesion in the mesencephalon (83, 115, 116). The effect on the muscle is said to be mediated either through the autonomic nervous system or by the endocrine glands. Recent evidence that sympathetic nervous fibers produce their effects by the liberation of either acetylcholine or an adrenalin like substance makes it difficult to understand how the sympathetic nervous system could

affect a muscle so as to produce myotonia. Acetylcholine is believed by many to be the normal agent of neuromuscular transmission in skeletal muscles and adrenalin has been shown to decrease myotonia. It is possible but unlikely that acetylcholine liberated by the parasympathetic nerve fibers in some region of the muscle fiber other than the end plate is the cause of the myotonia, or that the sympathetic nervous fibers are continually liberating adrenalin in the muscle fibers and myotonia is the result of a decrease in this adrenalin liberation.

OCCURRENCE OF MYOTONIA

Myotonia congenita

Myotonia occurs in its most typical form in myotonia congenita. This rare disease is hereditary and transmitted as a single factor dominant. Affected members of the family transmit the disease to half their children, normal members of the family do not transmit the disease (101). The disease begins in the first or second decade of life, increases in severity for a while and then remains more or less stationary although periods of exacerbation and remission may occur. Some members of affected families may be so slightly affected that under normal conditions they are apparently symptom free and have difficulty only during periods of special stress, such as pregnancy, menstruation, or an acute infectious illness. Griffith (58) describes a woman who had difficulty with myotonia only during pregnancy, her son had typical myotonia congenita. Lord (89) tells of a woman who had a difficulty similar to her myotonic brothers only during the week before her menstrual period. Occasionally families are described in which the disease decreases in severity as the members grow older. Especially interesting in this respect is a myotonic family described by Statmuller (133) in which a 15 year old boy developed severe myotonia quite suddenly and then gradually improved, so that, when seen three years later the only evidence of his previous condition was the presence of mechanical and electrical myotonia in a few muscles. His 42 year old mother stated that she had the same difficulty and that it had started at the age of 8 years, it was greatly aggravated during her menstrual periods and pregnancies and gradually left as she grew older until she became practically free.

Most of the muscles of the body are usually involved but with vary-

ing severity Associated with the myotonia is a hypertrophy of the muscles which makes the patient look markedly athletic The strength of the hypertrophied muscles is not, however, in proportion to their size and may even be less than normal Various psychic derangements occur in the members of affected families but their importance has been questioned (101) Muscle atrophy is said to occur in a certain proportion of the cases but in view of the confusion of *myotonia congenita* and *dystrophia myotonica* in early literature, these cases must be looked upon with suspicion The disease is not fatal and before the beneficial effect of quinine was discovered these patients were able to manage quite well by avoiding sudden movements and "warming up" before attempting marked exertion Quinine greatly decreases the disability, its effect on the muscular hypertrophy has not yet been reported

Dystrophia myotonica (myotonia atrophica)

Evidence today indicates that dystrophia myotonica occurs much more frequently than myotonia congenita and should no longer be considered a rare disease Although dystrophia myotonica is transmitted as a dominant characteristic, this dominance is modified by "progressive inheritance", that is, the disease occurs at an earlier age (anticipation) and in more severe form (potentiation) in succeeding generations As a result of this progressive inheritance the parents of patients often appear to be normal, whereas, the children of patients develop the disease at an earlier age than the parents and the disease tends to disappear from families (107) In this disease myotonia is not as important as it is in myotonia congenita, because it is less widespread and not as disabling as many of the other symptoms Myotonia is present mainly in the hand grasps but also may occur in the muscles of mastication and the leg muscles, and may occasionally involve most of the muscles of the body Mechanical and electrical myotonia are more widespread than voluntary myotonia The most disabling feature of the disease is a progressive muscular atrophy which with its associated weakness is usually the symptom which brings the patient to the doctor The atrophy in its early stages shows a definite pattern, involving mainly the muscles of the forearm, the cleidomastoids, the facial muscles, the quadriceps, and

of the feet The atrophy is later more general A rather characteristic cataract is sometimes the earliest evidence of the disease and is found in most patients if a slit lamp examination is made Other important extramuscular symptoms include testicular atrophy, baldness, low basal metabolic rate, and occasionally mental changes (145) These patients, unlike those with myotonia congenita, frequently die as a result of lowered body resistance produced by the disease

Myotonia congenita intermittens and paramyotonia congenita

Since Eulenburg (43) in 1886 and Martius and Hansemann (93) in 1889 described families with hereditary muscular disorders which became evident only under the influence of cold, a number of such families have been described Although the characteristics of the muscular disorder in the various families apparently show a wide diversity, certain similarities in the occurrence and nature of the disturbance suggests a close relationship Points of similarity are as follows 1) The fundamental characteristic on the basis of which all of these families may be grouped together is the appearance of the disorder only under the influence of cold When the patients are warm they consider themselves perfectly normal No precipitating factor other than cold is admitted The relative change in temperature is more important than the absolute temperature Temperatures at which patients may have no symptoms in the winter will produce symptoms if the patient is suddenly exposed to them in the summer After the effect of cold has set in, it usually persists for several hours and is only relieved by the application of warmth 2) Heredity is marked in each case The type of heredity is, furthermore, very similar to that of Thomsen's disease which may safely be said to be a single factor dominant (101) Many of the authors remark on the occurrence of the disease only in the children of affected individuals, the children of normal individuals remain normal The percentage of affected individuals is also close to the 50 per cent which would be expected in this type of heredity In almost all cases the disease is manifest as far back as the patient can remember and is apparently present from birth This onset is somewhat earlier than is usual for Thomsen's disease 3) The muscles most often affected are those of the forearm and hand The facial muscles and those of mastication

are almost as commonly affected and the leg muscles are usually affected only in marked cold 4) Pains and paraesthesias are almost always absent

Although the muscle disturbances appear to be of diverse nature, careful study shows that the various types can be arranged in a series according to the response to cold This has been done in table 2 Before considering the table it is necessary to review the effect of cold

TABLE 2

	MYOTONIA CONGENITA	MYOTONIA CONGENITA INTERMITTENS	PARAMYOTONIA CONGENITA (SÖLDER-SCHOTT)	PARAMYOTONIA CONGENITA (EULENBURG)
Warm	Voluntary Myotonia Slight Weakness	No difficulty with voluntary move- ments	No difficulty with voluntary move- ments	No difficulty with voluntary move- ments
	Myotonic Reaction	No Myotonic Reaction (Myotonic Reaction?)	Myotonic Reaction	No Myotonic Reaction Decrease in electrical irritability
	Voluntary Myotonia usually increased	Voluntary Myotonia (At times no im- provement may oc- cur with repetition of contraction?)	Prolonged voluntary contractions appar- ently aggravated by repetition Spontaneous persist- ing contractions with stiffness of muscles	Spontaneous contrac- tions with stiffness, persistent in some muscles, transient in others
Cold	Moderate increase in weakness	Moderate weakness	Marked weakness which increases with repetition of con- traction	Very marked weakness almost to paralysis
	Myotonic Reaction	Myotonic Reaction	Myotonic Reaction	No Myotonic Reaction Marked decrease in electrical irritability

With minor degrees of cold the myotonic reaction is probably increased With very severe cold the muscle may lose its irritability to mechanical and electrical stimuli.

on normal individuals and on patients with myotonia That some difficulty in movement results from the action of cold in normal individuals is well known Sölder (131) has shown that the difficulty consists of an appreciable decrease in strength, a slowness of contraction especially evident during relaxation, and some decrease in irritability to the faradic current In myotonia a definite decrease in strength occurs which is probably more marked than in normal individuals Voluntary myotonia is usually increased The effect

of cold on mechanical and electrical myotonia has not received much attention but from the work of Burger and Schellong (23) on myotonia congenita, Nylm (102) on dystrophia myotonica and Schott (123) on paramyotonia, the following changes probably occur. Moderate cooling leads to an increase of mechanical and electrical irritability and an increase in myotonia. Marked cooling results in a decrease to total absence of the mechanical and electrical irritability. These effects of cold on myotonia are tabulated in table 2. The myotonic muscle is thus affected by cold in the same direction as normal muscle and although this effect is somewhat greater in degree than in the normal muscle, it is not severe enough to constitute a marked abnormality. In those individuals whose symptoms are evident only under the influence of cold, however, the increased sensitivity to cold constitutes the most important defect. The manner in which this sensitivity to cold manifests itself apparently varies with other changes in the muscles. 1) In some muscles the reaction to cold consists in spontaneous contractions which are associated with and followed by marked weakness. 2) In some muscles the reaction to cold consists in a myotonic disturbance. 3) In some muscles the reaction to cold is a combination of (1) and (2). If the various families which have been reported are now examined, it is evident that they fall very nicely into these three groups.

In the family described by Eulenburg (43, 44) the reaction of cold was that of spontaneous contractions and marked weakness. Delprat (38) has described a similar family and the American family reported by Rich (108) is apparently of the same type. The essential characteristics of this condition are shown in table 2. In warm weather the patients have no muscular difficulty. In cold the muscles of the forearms and hands, face, and occasionally of the legs become stiff, and if the effect is marked, spontaneous persisting contractions occur. In some regions the spontaneous contractions last only a short time and are followed by a state of marked weakness. This paralyzing weakness is the outstanding symptom. The condition usually lasts for several hours and is relieved only by warmth. A myotonic reaction is not present either in warmth or in the cold. The electrical irritability of the muscles is somewhat decreased at normal temperatures and markedly decreased in the cold. That this condi-

tion differs from myotonia but is closely related is well shown by Delprat's family. Two members of a family in which weakness and stiffness of the muscles occurred under the influence of cold, developed typical pictures of myotonia congenita. The patients definitely separated their troubles into the one produced by cold which they had had since birth like the rest of the afflicted members of the family and the stiffness which had come on during puberty and was present only on initiating movements.

In the patients described by Martius and Hanseemann (93) and especially by Serog (125), cold produced a myotonic disturbance. These patients had no difficulty in warm weather, but under the influence of cold developed a definite voluntary myotonia. Although Martius and Hanseemann state that there was no improvement in the myotonia with repeated movements, Serog's finding that the myotonia decreased with continued movement is to be expected. The strength of the contraction was not greatly decreased. A myotonic reaction was present in the cold but not in the warmth. It is probable, however, that some of the members of the family would also show the myotonic reaction in the warmth. Martius and Hanseemann called the condition "myotonia congenita intermittens" and Serog called it "paramyotonia congenita." From the standpoint of priority and appropriateness "myotonia congenita intermittens" is the preferable designation for this condition.

Sölder (131) and Schott (123) have described families under the title of paramyotonia congenita which differ from the family described by Eulenburg. In the members of their families cold produced both the marked weakness and the myotonia, that is, the combined type of reaction. As in the other families, the patients had no difficulty with voluntary movements in warm weather. Even in warm weather, however, many of the members had a myotonic reaction of greater or lesser degree. In cold the patients had marked difficulty with voluntary movements consisting of a prolongation of voluntary contractions and a marked weakness of the muscles. The weakness of the muscles increased rapidly with repetition of movements. This increasing weakness may account for the fact that the prolongation of contractions also became more marked as the movements were repeated. The muscles felt tight and firm and with more marked

cold spontaneous persisting contractions and marked paralyzing weakness set in. The myotonic reaction was somewhat increased with smaller degrees of cold but with more marked cold the muscles lost all or nearly all irritability. Improvement occurred only with warmth. It is clear that definite differences exist between this condition and that described by Eulenburg although both have been called paramyotonia congenita. This term probably fits the disease described by Solder and by Schott better than that described by Eulenburg but it was first used by Eulenburg. A new designation might be considered for one of the diseases but it is probably best to call both diseases "paramyotonia congenita" and qualify them as "paramyotonia congenita-Eulenburg" and "paramyotonia congenita-Solder-Schott." Table 2 shows the important characteristics of each.

Congenital localized myotonia

Garra and Garra (53) describe a patient who had from birth a myotonia localized to the muscles innervated by one facial nerve. This is the only case of this type that could be found in the literature.

Myotonia acquisita

A number of cases have been described in the literature in which myotonia is stated to have followed some trauma or acute infectious disease and to have occurred in individuals at a late age and without a hereditary background. Talma (138) first designated these cases "myotonia acquisita." Recently Krabbe (76, 77) has reported a case and collected from the literature 34 cases of myotonia acquisita. He concluded from the study of these cases that "acquired myotonia must be considered as an independent disease, entirely different from Thomsen's disease, the congenital myotonia, which presents similar symptoms but which is a disease of an altogether different origin." He also concluded that acquired myotonia "does not appear ever to be produced by diseases which attack the central nervous system, such as syphilis, arteriosclerosis, or encephalitis, but seems in a large number of cases to be caused by polyneuritides or diseases which attack the peripheral nerves and muscles producing an hypertrophy of the sarcoplasm." Eleven of the articles referred to by Krabbe were read; in these eleven articles 14 patients were described. The articles read

were chosen only on basis of easy accessibility. In six (30, 51, 143, 145, 146, 150) of the 15 patients described in these articles the reaction of the condition was not typical of myotonia, as 1) involuntary spasms, generalized spasms, no improvement with exercise were not muscle stiffness when the patient was at rest one or more of these in each case showed that the condition was not myotonia. This is further confirmed by the fact that in not one of the five patients in which electrical tests were made was a myotonic reaction found. It is possible that the myotonic reaction may occasionally be absent for a time in very mild cases of myotonia, but the absence in every case here is significant. In the 8 other cases the following is found. In a 12 year old boy (150) inheritance was in no way excluded. In one patient 40 years of age (136) the myotonia was associated with the typical muscular atrophy of dystrophia myotonica—sternocleidomastoids, hands, feet, orbicularis oculi. In another adult (1) the sternocleidomastoids had begun to atrophy. In one case (118) a fairly typical voluntary myotonia and a somewhat more typical myotonic reaction were associated with marked muscle tenderness, spasms, paraesthesias, and pain, interpretation of this case is difficult. The report on one patient (148) is too scanty to evaluate. This leaves only the three patients reported by Jacoby (68). They apparently had definite myotonia with no heredity but nothing in two of these cases is incompatible with the diagnosis of dystrophia myotonica before the stage of atrophy. The third patient appears to have had a temporary myotonia. It is evident that little is left of the 14 so called cases of myotonia acquisita. There is no reason for believing that examination of the remaining 20 cases found by Krabbe in the literature would show anything different.

Few cases of myotonia acquisita will be found if strict criteria for the presence of myotonia are applied. This is particularly true if it is remembered that in families with myotonia congenita some of the members may be so slightly affected that the action of some noxious agent is necessary for the myotonia to become evident and that in dystrophia myotonica the myotonia may be the first symptom and may at times be very widespread. The existence of acquired myotonia cannot be entirely denied, but its occurrence must be rare.

It is certainly possible that some acute infectious diseases precipi-

tate or aggravate myotonia in individuals with an inherited defect. A patient seen by the author dated her illness, consisting at that time only of myotonia, from an attack of typhoid at the age of 23 years. If she had been seen at that time she could certainly have been said to have myotonia acquisita. Seen, however, at the present time with the typical atrophy of dystrophia myotonica, both lenses removed for cataract, and with cataracts in 34 and 31 year old sisters, no question exists of the diagnosis of dystrophia myotonica.

The 24 year old boy described by Krabbe (76) with no hereditary background, slowness of movements, muscle hypertrophy and myotonic reaction presents the syndrome of hypothyroidism, muscular hypertrophy and myotonia to be described.

Syndrome of hypothyroidism, muscle hypertrophy and myotonia

A number of patients are reported in the literature in whom hypothyroidism, muscle hypertrophy, and myotonia are associated to form strikingly similar clinical pictures. A description of these patients will make this clear.

In 1903 Shmidt (126) reported the occurrence of myotonia in a patient with no hereditary background for its manifestation but with myxedema of about $4\frac{1}{2}$ years duration. Shortly after the onset of the symptoms of myxedema the patient had noticed the occurrence of muscular spasms in association with voluntary movements. Examination revealed a typical voluntary myotonia in addition to the classical evidences of myxedema. The myotonia was evident in all the muscles of the extremities, the muscles of the trunk and neck, the muscles of mastication and the tongue. The mechanical and electrical irritability of the muscles was increased. The reflexes were normal. The myotonia as well as the myxedema improved with thyroid therapy, returned when the thyroid was stopped for a month, and left again with resumption of thyroid. Shmidt concluded that "the simultaneous development and parallel changes of both diseases and the definite improvement of both resulting from thyroid treatment, force a conclusion that both have the same cause—abnormal functioning of the thyroid gland."

During 1917-18 Kramer (78, 79, 80) in several short reports described three unusual cases of myxedema. The picture of myxedema

was clearly developed, with marked slowness and difficulty in movement, narrow palpebral fissures, coarse speech, loss of hair, dry pasty skin, and "myxedema heart." These patients also had a marked hypertrophy of the muscles, especially those of the extremities. The hypertrophy was associated, however, with a decrease rather than an increase in strength. There was no voluntary myotonia. The patellar and Achilles reflexes were easily elicited but were sluggish, the slowness involving the contraction as well as the relaxation. The muscles contracted readily on mechanical stimulation but here again with a slowness of contraction and some slowness of relaxation. Both direct and indirect faradic and galvanic stimulation produced prolonged contractions. The symptoms of myxedema and the prolongation of the muscle contractions disappeared following thyroid administration. Kramer does not state whether the muscle hypertrophy showed any change.

In 1921 Slauck (127) stated that in two cases of myxedema he found electrical reactions similar to those described by Kramer and emphasized the similarity to the myotonic reaction. He concluded that "if these observations are right (the similarity of myxedematous and myotonic muscles in their behavior to the electrical current) then we should find in severe untreated cases of myxedema, myotonic symptoms." He also reported the occurrence in congenital myxedema of a hypolemmal layer of striated circular fibers such as had been described by Heidenhain in dystrophia myotonica and correlated the similarity in electrical behavior with this pathological finding. Later (128), having failed to find them in some patients with Thomsen's disease, he decided against their importance.

In 1924 Chaney (27) again described the abnormally prolonged character of the tendon reflexes in myxedema which had been seen by Kramer. From graphic records he described the contraction as occurring with about normal rapidity, but persisting for as long as a second and relaxing slowly. Although Chaney apparently obtained this prolongation in all of his patients with myxedema, other workers have found it only occasionally. Eckerström (40) in 1936 also reported the presence of the prolonged Achilles tendon reflex in a woman with myxedema. He found it in no other reflexes and stated that no myotonic reaction occurred with the faradic current.

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In 1929 Weitz (147) described a 44 year old doctor who, following x-ray radiation and thyroidectomy for hyperthyroidism, became definitely myxedematous. With the development of myxedema the skeletal musculature became more bulky and more firm, especially in the calves of the legs, but the muscle strength was not increased. On many movements and especially on sudden movements painful cramps lasting 6 to 10 seconds occurred in the muscles used. During these cramps the affected muscle was board-like in hardness. On passive movement and on slow active movement no pain or spasm occurred. If certain movements were repeated, especially opening and closing of the hands, the first movements did not occur as rapidly as later movements but the difference was not marked. Striking the muscles produced elevations (idiomuscular?) lasting a number of seconds. The muscles were very irritable mechanically and percussion of small muscles produced contraction of the entire muscle. Weitz does not state whether the contractions were slower than normal. Electrical examination of the muscles revealed a moderate hyperirritability but apparently no myotonia. The muscular symptoms were aggravated by cold and fatigue. The reflexes were not slow. After thyroid treatment the muscles became softer, the muscle cramps stopped, and the slowness of contraction on voluntary and mechanical stimulation left with the symptoms of myxedema.

In 1933 Krabbe (76) described as a case of acquired myotonia a 24 year old man who in addition to his muscle symptoms showed a sallow color, dry skin, progressive fatigue, slow movements, slow speech, sensitivity to cold and basal metabolic rate 67 per cent of normal. He also had a marked muscular hypertrophy. At times when he flexed his fingers vigorously, he had trouble in extending them again. On electrical examination there was a marked myotonic reaction and diminished faradic and galvanic excitability. A piece of leg muscle removed and examined microscopically showed no abnormality except a slight increase in the volume of the muscle fibers. He was given thyroid extract and improved considerably, the power and rate of movement increased and the muscles seemed to diminish in bulk.

In 1935 Garcin et al (52) described a 28 year old man in whom there was a simultaneous appearance and the parallel evolution of the syn-

drome of Thomsen's disease and myxedema. The muscular dystrophy was characterized by a marked hypertrophy of many of the muscles and the presence of myotonia. A stiffness of the first movements improved with repetition. The degree of stiffness was not comparable to that seen in myotonia congenita. In addition, painful cramps occurred on sudden movements in muscles in which no voluntary myotonia could be determined and in myotonic muscles even after the initial stiffness had passed. Marked myotonic contractions following percussion were seen in many muscles. The electrical reactions in this patient were studied by Bourguignon and Garcin (13) who concluded that the myotonia although definitely present was "far from having the characteristic slowness of the myotonia in the myopathies." The patient died of pneumonia, apparently before the effect of thyroid therapy could be determined.

In 1935 Debre and Semelaigne (36) described a child two years of age whose intellectual and physical development appeared to have been more or less stationary after the first few months of life. Examination at two years revealed a general hypertrophy of all the muscles in the body and the tongue. A pronounced muscular hypertonia, stiffness of the limbs, and difficulty in bending or straightening were also noted. The reflexes were feeble but present. The psychic development was almost nil. Certain findings suggested hypothyroidism, such as wrinkled forehead, flat nose, swollen eyelids, thick lips, large tongue, absence of hair on eyebrows and scalp, arrested physical growth, and mental deficiency. Thyroid was given with remarkable results. The muscular masses decreased almost to normal, the facies changed, the tongue became normal in volume, intelligence improved, movements became more rapid and precise, and the hypertonia left. Debre and Semelaigne believed that their case and the similar cases described by Bruck (21) in 1889 and by deLange (87) in 1934 presented a syndrome due to congenital athyroidism. These authors pointed out the following points of similarity on all of these cases: congenital origin, the general muscular hypertrophy and athletic appearance, permanent and paroxysmal muscular hypertonia, intellectual deficiency, arrested development and the fatal prognosis.

Poncher and Woodward (105) in 1936 reported the case of an infant who at five weeks began to have generalized tonic spasms associated

with cyanosis When examined at 5 months of age he had the general appearance of an infant Hercules because of the marked enlargement of the muscles all over his body The muscles were unusually firm and showed a localized dimpling and sustained contraction on mechanical percussion The reflexes were normal During the spastic attacks the muscles over the entire body contracted and the patient became rigid and cyanotic An entire attack lasted from sixty to seventy-five seconds Galvanic stimulation of the muscles showed normal or somewhat increased irritability with ACC equal to or slightly greater than CCC Galvanic stimulation resulted in a slow, wormlike contraction which persisted for almost a minute after the stimulus ceased Because the infant did not show the normal creatinuria of infancy he was treated with thyroid The result was striking the myotonic reaction left, the spastic spells stopped, the muscular hypertrophy decreased, and urine excretion of creatine became normal In view of what has been said about myotonia, it is evident that the spasms in this patient cannot be considered as an evidence of myotonia, they in no way correspond to what has been said of myotonia They must be correlated with the muscle cramps which have been described in several of the other cases In regard to the question of hypothyroidism the authors state "Epiphysial development, the texture of the hair and skin, the muscular development and tone, the blood cholesterol and other factors were against a diagnosis of hypothyroidism The delayed development, the large thick tongue and the absence of creatinuria were the only manifestations compatible with such a diagnosis " The argument for hypothyroidism is greatly improved if to those features compatible with hypothyroidism is added the highly significant fact of relief of the symptoms with thyroid therapy

Valdés Díaz (141) reported the case of a Negro male infant who at three months of age had generalized muscular hypertrophy and a Herculean appearance When the patient was treated with thyroid, the myotonic symptoms which were present and the muscular hypertrophy disappeared

Nevin (quoted from Poncher and Woodward (105)) saw a girl of 17 years in whom the diagnosis of myotonia congenita was made because of enlargement of the muscles and myotonia Because of a

history of cretinism, thyroid which had not been given for some time was administered to the patient. This resulted in such improvement in the muscle findings that it was no longer possible to consider the case one of myotonia congenita. Studies of action currents in the muscle also led Nevin to believe that the disorder was different from Thomsen's disease.

Maas (91) states that Dr. Martin observed a case in the National Hospital of a woman who had a rough dry skin and myotonic reac-

TABLE 3

Syndrome of Hypothyroidism, Muscle Hypertrophy and Myotonia—Summary of Patients Reported in the Literature

AUTHOR	AGE	SEX	HYPOTHYROIDISM	MUSCLE HYPERTROPHY	VOLUNTARY MYOTONIA	MECHANICAL MYOTONIA	ELECTRICAL MYOTONIA	SPASMS OR MYOTONICITY	PROLONGED REFLEXES	IMPROVEMENT WITH THYROID
Schmidt (126)	40	M	+	?	+	?	?	0	0	+
Kramer (78, 80)	30	M	+	+	0	+	+	0	+	+
Kramer (79, 80)	?	?	+	+	0	+	+	0	+	+
Kramer (79, 80)	?	?	+	+	0	+	+	0	+	+
Slauck (127)	?	?	+				+			
Weitz (147)	44	M	+	+	+	+	0	+	0	+
Krabbe (76)	24	M	+	+	+	+	0	0	0	+
Garcin et al. (52)	28	M	+	+	+	+	+	+	0	
Debré and Semelaigne (36)	Infant	F	+	+			0	+	0	+
Poncher and Woodward (105)	Infant	M	+	+	?	+	+	+	0	+
Valdés Díaz (14)	Infant	M	?	+	+	+	+			+
Nevin (105)	17	F	+	+	+	+	+			+
Maas	?	F	+		+	+	+			+

* Report states only that myotonia was present, type not mentioned.

tions on electrical excitation, mechanical excitation and active movements, these completely disappeared after treatment with thyroid extract.

The remarkable uniformity of the clinical picture of these cases is evident from an examination of table 3 in which the findings have been listed.

The evidence for *hypothyroidism* is clear cut in practically all cases. In the patient described by Poncher and Woodward some doubt could arise but, as stated, important evidence points to the presence of a

thyroid insufficiency In the case reported by Valdés Díaz the original article could not be examined and Poncher and Woodward do not state whether any evidences of hypothyroidism were present The improvement with thyroid therapy was, however, significant In some cases the hypothyroidism was congenital, in one it followed x-ray radiation and thyroidectomy, and in the remainder it occurred spontaneously in later life

Muscle hypertrophy was a striking feature in most of the cases and often the condition which resulted in the case being reported It was usually quite generalized but often more marked in the extremities The muscle strength did not correspond to the muscle bulk and was often less than normal The muscles were very firm

Voluntary myotonia was a very minor symptom in most cases Kramer stated that none was present in his three cases Weitz's patient had it in very small degree The patient described by Garcin et al had definite myotonia but the authors state that it was much less than ordinarily seen in myotonia congenita The muscle spasms which are described by Poncher and Woodward are not myotonic *Mechanical myotonia* was present in every case when looked for An *electrical reaction* resembling that seen in myotonia was described in all but two cases After careful examination, Bourguignon and Garcin (13) came to the conclusion that although the myotonic reaction was definitely present, it did not resemble that usually seen in myotonia because of its much shorter duration Kramer's cases apparently showed a definite prolongation of contractions following indirect galvanic stimulation, this is usually not found in myotonia

In summary regarding the presence of myotonia it may be stated that in the one case very carefully investigated by those familiar with the condition, a definite myotonia to all forms of stimulation was found but the myotonia differed from that in true myotonia congenita by its shorter duration Voluntary myotonia is only slight and often absent The mechanical myotonia is most evident and marked Electrical myotonia is usually present but differs from the electrical myotonia seen in myotonia congenita in minor details Some question exists as to whether the reaction is a true myotonia in the sense that it represents the same type of muscle change as is found in myotonic conditions described Some question also exists as to whether the

dissociation in the occurrence of the various forms of myotonia represents a true absence of some forms or their presence in such a small degree that they were overlooked

The *spasms* are probably associated with the hypertonicity of the muscles and were seen mainly in the infants. The spasms were present in at least three cases and were evident as painful contractions of one muscle group or the muscles of the entire body coming on usually with sudden or forcible movements. They are definitely not of myotonic nature and probably have no relation to true myotonia. On the other hand, what appears as myotonia in these cases may possibly be an expression of this hypertonic condition of the muscles. The hypertonicity of the muscles in the case of infants was especially evident as a resistance to passive movement. A central origin of this hypertonicity is quite possible.

Prolongation of the reflexes was evident in Kramer's cases and has been reported in other cases of myxedema in which the other muscle symptoms described here were either not present or not evident enough to attract attention. The reflexes were stated in most cases to be definitely lively, however, in one sense a reflex may be lively, that is easily elicited and marked in extent, and still be somewhat prolonged, so that it is possible that more attention paid to the type of reflex may show the presence of prolongation to be more common.

In every case where *thyroid* was given, marked improvement occurred not only in the symptoms of myxedema but in the muscle symptoms. The myotonic phenomena, the muscle hypertrophy, and the muscle cramps were alleviated.

The marked and complete response to thyroid appears to offer a solution to the nature of these cases. Individuals with myotonia congenita rarely show evidence of hypothyroidism, and are not benefited by thyroid therapy. These individuals with hypothyroidism and myotonia, on the other hand, become normal when given thyroid. Since thyroid alone can make these patients normal, and the absence of thyroid produces the muscle symptoms along with the other symptoms of myxedema, no other choice seems open than to conclude that the muscle symptoms are an evidence of thyroid deficiency in these individuals. Why doesn't thyroid deficiency produce these symptoms in all individuals? It is likely that similar symptoms in

do occur in most cases of marked myxedema and that closer investigation will reveal them. The marked syndrome probably occurs only in individuals who have a certain inherited tendency to the manifestation of such symptoms. This concept receives plausibility from the finding that some individuals with an inherited tendency to myotonia may exhibit myotonia only at certain times. The inherited tendency may not be of the same nature as the one which results in myotonia.

SUMMARY

Whether produced by nerve impulses, electrical current (electrical myotonia) or mechanical percussion (mechanical myotonia), the myotonic contraction persists for an abnormally long time after the stimulus producing it has ceased. The persistence of the contraction is evident as a slowness of relaxation of the muscle. Nerve impulses producing myotonic contractions are almost always of voluntary origin (voluntary or active myotonia).

In a series of contractions following a period of rest voluntary myotonia decreases in successive contractions until it is usually no longer evident, correspondingly, myotonia is worse after a period of rest. Within limits myotonia increases with increase in force of contraction.

The myotonic contraction produced by nerve impulses is of dual nature, consisting of two superimposed components: one, a voluntary contraction of the usual type starting and stopping as desired by the will, the other, a persisting contraction setting in at the time of the voluntary contraction and lasting for a definite time regardless of the duration of the voluntary component. Both components probably involve the same muscle fibers.

In addition to the slowness of the phase of relaxation, voluntary myotonic contractions occasionally show other abnormalities. The phase of contraction may show a slowness which is aggravated by cold and by calcium. In a series of contractions the second and several succeeding contractions are occasionally weaker than the first contraction.

Excitement, fright, and other emotional stimuli increase voluntary myotonia. Neither venous congestion nor complete obstruction of

the circulation for several minutes appreciably influence voluntary myotonia. Cold usually increases voluntary myotonia but may occasionally decrease it.

Myotonia has been shown to be influenced by the following drugs. Quinine and quinidine markedly decrease myotonia. Epinephrine decreases myotonia. Insulin decreases myotonia when it produces symptoms of hypoglycemia. Calcium decreases myotonia. Prostagmin and potassium chloride increase myotonia.

Myotonic muscles usually show an increased irritability to mechanical stimuli. The contraction and especially the relaxation of myotonic muscles following mechanical stimulation are prolonged.

Erb's original description of the reaction of the nerves and muscles of myotonic patients to electrical stimuli has been modified only in minor details by later investigators.

No change in the composition of the blood or in the metabolism of patients with myotonia has been definitely correlated with the myotonia.

Hypertrophy of the muscle fibers, increase in the sarcolemma nuclei, and an indistinctness of transverse striations have been the most commonly reported pathological changes in myotonic muscles.

Investigations for the presence of action currents during myotonia have given contradictory results and failed to locate the defect in myotonia. The similarities of the properties of myotonia to those of Tiegel's, veratrine, neuromuscular, and acetylcholine contractures suggest that myotonia is a contracture and that the defect in myotonia is, therefore, probably in the muscle. This conclusion is supported by evidence obtained by analyzing that property of myotonia which has been called "dual nature of the myotonic contraction."

A review of the relation of the endocrine glands to myotonia indicates that although myotonia is influenced by the various known hormones it is probably not produced by any of them.

In the present state of our knowledge of the relation of the autonomic nervous system to skeletal muscle, it is difficult to understand how a defect of the autonomic nervous system could produce myotonia.

Myotonia occurs classically in myotonia congenita, but most frequently in dystrophia myotonica. In the rare conditions, myotonia

congenita intermittens and paramyotonia congenita-Solder-Schott, myotonia is evident only under the influence of cold. Myotonia does not occur in paramyotonia congenita-Eulenburg. Myotonia acquisita, that is, myotonia without an hereditary background, is rare. A fairly large group of patients presenting a syndrome of hypothyroidism, muscle hypertrophy and myotonia have been reported in the literature.

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